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CHARACTERISTICS OF FRESH HUMAN CARTILAGE

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IN RECONSTRUCTIVE SURGERY there is a great demand for a supporting material for the correction of contour defects. This substance must be readily available in large quantities, must be simply prepared for use and readily cut to the desired shape, must cause no reaction in adjacent tissues, must resist absorption and infection, must have little tendency to perforate through overlying skin or mucous membrane, especially when subjected to repeated minor trauma, and must have no marked tendency to distortion. Bone is an excellent supporting tissue, but, when transplanted, must be in contact with bone of the host to maintain its functional integrity. If adoption of the graft by the host is incomplete because of poor apposition with the bone of the host or absence of the stress mechanisms which stimulate its growth, the graft will be unsatisfactory. In addition, bone is rather difficult to shape, especially in fine work, and, of course, is of no value in the reconstruction of joints. Foreign materials, such as plastics and metals, are too frequently extruded, especially when in a subcutaneous or submucosal position. Autogenous cartilage fulfills many of these criteria very well, but in the repair of gross defects a secondary deformity of the donor site is often produced. In addition, there is prolongation of the operative time and also the possibility of entering the pleural cavity. Although autogenous cartilage has a definite tendency to become distorted, this can be prevented by symmetric carving or by cross cutting. Heterogenous cartilage is frequently absorbed, with loss of its supporting effect, and replaced by fibrous tissue.

With these problems in mind, an investigation of homogenous cartilage grafts was undertaken. It was decided to investigate the potentials of both viable and nonviable homogenous cartilage as a supporting material since the clinical impression exists that nonviable cartilage is frequently replaced by fibrous tissue and absorbed.

Because it is impractical to transfer cartilage directly from the fresh cadaver to the patient or volunteer host, it was necessary to find a storage medium which would maintain the viability of the cartilage prior to transplantation. In addition, it was necessary to select other media to render the cartilage nonviable for these comparative studies. The media which were selected to maintain optimal viability were plasma, as

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a liquid environment, and air. Merthiolate-saline solution was chosen to render the cartilage nonviable by virtue of its known toxic effect on the cellular enzyme systems and its popularity as a storage medium.

It was first necessary, of course, to measure the effects of these storage media on the viability of cartilage by quantitative studies. Since viability is such a nebulous quality and so difficult to quantitate, it was decided to carry out a wide range of examinations, including supravital stains, metabolic studies, histologic examinations, and the study of electrolyte and water exchanges in order to have a baseline for comparison. These examinations were carried out first on fresh human cartilage, and the results are recorded in this article. Identical studies were repeated on cartilage stored in merthiolate, plasma, and in air. In addition, these examinations were again carried out on cartilage stored in these media and then transplanted in human volunteer hosts for about 2 years.

From this pilot study some conclusions were drawn as to which of the media examined was best suited to preserve viability and the importance of viability in regard to the maintenance of the integrity of cartilage as a supporting tissue.

METHODS

Costal cartilage was removed from fresh cadavers by using aseptic technique, placed in a sterile bottle containing 10^6 units of aqueous penicillin and 1 gram of streptomycin in 300 cubic centimeters of normal saline, and refrigerated at 3 to 5 degrees C. for 24 hours. The cartilage was then stripped of all soft tissue, including the perichondrium, cut into standard lengths, placed in sterile containers, capped, and refrigerated at 3 to 5 degrees C.

Supravital stains. The staining technique is essentially that of Kredel and Roberts. The specimen was immersed for a period of 48 to 60 hours in a 1:10,000 aqueous solution of neutral red which had been buffered with Tyrode's solution. The cartilage block was then removed from the stain, and cross sections were cut with a microtome. The sections were then mounted in a few drops of Tyrode's solution upon a glass slide and immediately examined microscopically. The sole criterion for cellular viability was the presence of the characteristic red-staining intracytoplasmic granules or droplets (Fig. 1). Degenerating cells take up the dye quickly, the nucleus alone staining a diffuse reddish-orange color. Dead cells fail to exhibit any coloration. Counts were made with a Howard micrometer disc of 8 to 10 areas, selected at random, on each slide. The counts were averaged for each slide and results tabulated under 3 headings: central cellular viability, peripheral cellular viability, and general cellular viability. Significant data of cellular longevity are considered to fall under "general" viability; the central and peripheral counts were made merely for purposes of comparison, in an attempt to evaluate any positional factors which may influence the length of time the cells remain viable when stored.

Metabolic studies. Respiration and anaerobic glycolysis were studied by usual Warburg manometric methods. The costal cartilage was sliced in cross section to a thickness of about 0.4 millimeter. This appears to be near the "limiting thickness" for cartilage. An average of 202 milligrams of sliced cartilage was placed in each Warburg flask. The suspending medium for studies of oxygen consumption consisted of 2.7 milliliters of Krebs-Ringer solution buffered at *p*H 7.6 with a phosphate buffer. In the center well of each flask was placed 0.2 milliliter of 10 per cent sodium hydroxide solution. The flasks were equilibrated with 100 per cent oxygen for 15 minutes. Aqueous methylene blue (0.2 ml., 0.001 molar) was added to some flasks to gain an estimate of the substrate-activating component of the respiratory system in cartilage. The suspending medium for the investigation of anaerobic glycolysis consisted of 2.5 milliliters of Krebs-Ringer bicarbonate solution and 0.2 milliliter of a 10 per cent glucose solution. The manometers were equilibrated with a mix-

ture of 95 per cent nitrogen and 5 per cent carbon dioxide for 15 minutes. The Warburg flasks were maintained at 37.5 ± 0.01 degrees C. and oscillated 120 times per minute. After equilibration for 15 minutes, readings were taken at 10 minute intervals for 1 hour. Respiration (QO_2) and anaerobic glycolysis ($Q_G^{N_2}$) were expressed as cubic millimeters of gas per milligram of dry weight of tissue per hour. The average length of time between the death of the donor of the tissue and the metabolic studies on the cartilage was about 15 hours. The metabolic rates reported are essentially "normal" rates, since the metabolism of cartilage, in particular its oxygen consumption, varies only slightly (−14 per cent) for approximately 10 days after the death of the individual, when the cartilage is stored in Ringer's solution or plasma.

Histologic method. The cartilage block was fixed in formalin, embedded in paraffin, and sectioned by microtome at 6 microns. The sections were cleared of paraffin, stained by Harris' hematoxylin and eosin method, then mounted for microscopic examination. In addition, Verhoeff, Schiff, and von Kossa stains were performed by the usual method on many of the cartilage specimens. The analysis of the sections was divided into the following categories: (1) normal, (2) pyknotic, (3) karyolytic, and (4) "dropped-out" cells (absence of cytoplasmic material in lacunae). In addition, cell counts of specimens of varying age were made with a calibrated Howard micrometer disc. The values reported are average values obtained from 20 to 25 areas per section, each section representing 2 square millimeters. Areas having the appearance of fibrous or connective tissue with blood vessels were seen and measured in the following manner: a histologic section of cartilage was placed in a photographic enlarger and the image projected at a magnification of 13.25. The periphery of the image and the centrally placed islets of fibrous or connective tissue were traced and their area determined by a planimeter.

TABLE I.—OXYGEN CONSUMPTION, METHYLENE BLUE OXYGEN CONSUMPTION, ANAEROBIC GLYCOLYSIS, DRY WEIGHT, AND SODIUM AND POTASSIUM CONTENT OF HUMAN COSTAL CARTILAGE

Determinations	*No. of individuals*	*No. of determinations*	*Average values* ±	*(S.E.)**
QO_2	8	11	−0.017 ±	0.006
$Q_{O_2}^{Mb}$	6	12	−0.032 ±	0.009
$Q_G^{N_2}$	21	120	+0.053 ±	0.004
Per cent dry weight	63	200	37.8 ±	0.33
Sodium	22	64	172.46 ±	11.06†
Potassium	22	64	20.30 ±	1.51†

*Values are for individuals above 14 years of age.
†mEq./kgm. of fresh cartilage.

Only the central islands of this connective tissue were measured since the peripheral areas could not be distinguished from irregularities in contour produced by the preparation of the tissue. Areas of fibrous or connective tissue were expressed as the percentage of cross sectional area of the cartilage block.

Electrolyte and water exchange. Samples of cartilage weighing about 1 gram were placed in silica crucibles and dried at 100 to 105 degrees C. for 24 hours. After reweighing (to determine the water content) the cartilage was ashed at 550 degrees C. for 36 hours. The residue was suspended in 0.1 normal hydrochloric acid and diluted with lithium chloride solution. Analyses for sodium and potassium were made on the diluted sample by the use of lithium internal standard flame photometry.

RESULTS

Supravital stains. Almost all of the cells appeared viable in over 100 pieces of fresh cartilage examined. The limits of variation were from 95 to 99 per cent viability by count, with an average of 98 per cent.

Metabolic studies. The oxygen consumption of cartilage, taken from 8 cadavers, was −0.017 ± 0.006 (S. E.) (Table I). The oxygen consumption in the presence of methylene blue was −0.032 ± 0.009, as studied in 6 cadavers. Since these two values so closely approached the limits of accuracy of this

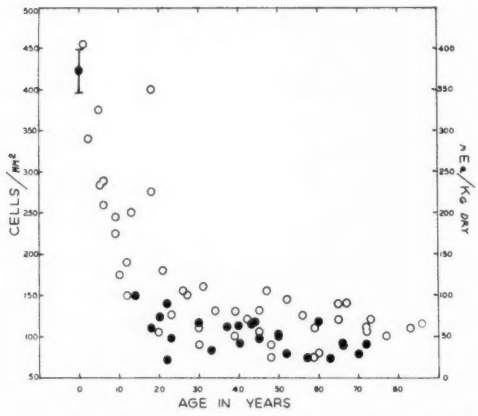

FIG. 2. The effect of age of the individual on the chondrocyte count (O) and the potassium content (●) of human costal cartilage. The potassium dot at zero time is from Iob and Swanson. The bars represent 1 standard deviation.

technique, it was thought that continued investigations along these lines would not be profitable. However, the anaerobic glycolysis was found to be $+0.053 \pm 0.004$ in 21 cadavers. Since this value was well within the limits of accuracy of our method, primary reliance was placed upon this parameter (Table I).

Histologic studies. The examination of histologic sections from fresh cadavers revealed a considerable degree of cellular degeneration as shown by the following average values: age of donor, 28 years; normal cells, 33.2 per cent; pyknotic cells, 35.1 per cent; karyolytic cells, 11.4 per cent; "dropped-out" cells, 20.3 per cent; "fibrous tissue" areas, 0.093 per cent. The number of cells per square millimeter decreases markedly over the life span of the human (Fig. 2).

Electrolyte and water exchange. The dry weight of adult human costal cartilage is high, compared to other tissues, being 37.8 per cent (Table I). The water content of human costal cartilage exhibits a marked variation with age (Fig. 3). At birth, cartilage contains about 90.1 per cent water. This value is somewhat higher than reported by Iob and Swanson, but the difference is possibly due to our removing the perichondrium. The decrease of water content with age is probably a reflection of the characteristic general body dehydration, and not a peculiarity of cartilage. The sodium and potassium contents of this tissue (Table I) are in agreement with values obtained in other species.

DISCUSSION

The characteristic reactions of living cells, degenerating cells, and dead cells to neutral red have been described in cytologic studies by many investigators. However, for successful application of this technique, 3 important features must be considered: the maintenance of hydrogen ion concentration slightly to the acid side of neutrality; the avoidance of toxic levels of dye concentration; and immediate examination of the slides after preparation, since the color reaction begins to fade within 15 to 20 minutes, possibly because of the *p*H changes on a cellular level. In the examination of a large number of cartilage sections prepared to exhibit varying degrees of viability, supravital stains were found to be reliable and constant. Although 1 to 5 per cent of the fresh cartilage cells were nonviable by this stain, these were all found in the periphery where they were subjected to injury in preparation.

The degree of cellular deterioration encountered in histologic sections of cartilage from fresh cadavers may be attributed to several causes: the age of the patient; the chronicity and debilitating effect of the patient's illness before death; the number of hours post mortem; and, lastly, the possible cellular injury sustained by relatively slow diffusion of the fixative. This last factor is confirmed by the observation of the presence of greater numbers of "normal" cells in the periphery of the cell blocks.

The presence of areas having the appearance of fibrous or connective tissue with blood vessels is probably explained by the passage of vessels of moderate size (10 to 50 microns) through the cartilage. The areas of connective tissue which were seen without

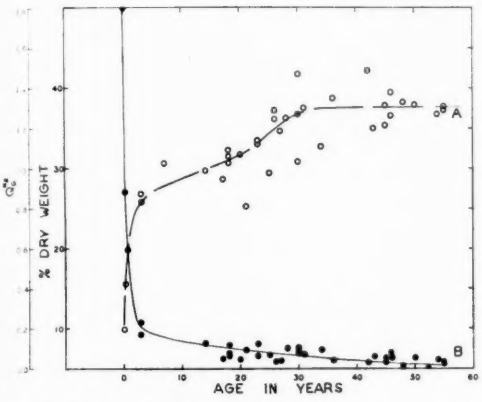

FIG. 3. The anaerobic glycolysis (shown by curve *B*) and the per cent dry weight (shown by curve *A*) of human costal cartilage as a function of the age of the individual.

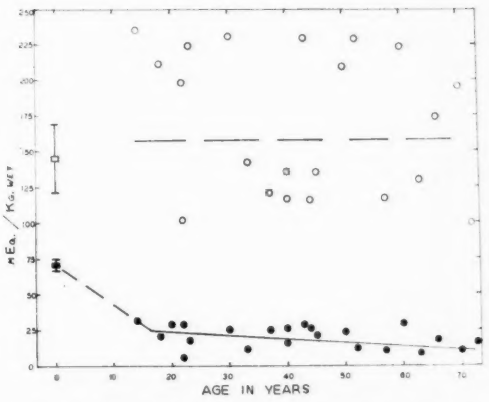

FIG. 4. The effect of age on the sodium (○) and on the potassium (●) contents of human costal cartilage. The rectangles at zero age are from Iob and Swanson. The bars represent 1 standard deviation.

such vessels were probably tangential or peripheral sections of these areas.

Both the oxygen consumption and the glycolytic activity of human cartilage are very low, being on the order of 1/100 to 1/500 of those for other human tissues. However, as shown by Bywaters, the anaerobic glycolysis calculated per cartilage cell is equal to that of other cells. Therefore, it is mainly the relative paucity of cells in cartilage which causes the low values of anaerobic glycolysis when calculated on a weight basis. It appears that the oxygen consumption of cartilage cells is still about 1/50 of that for other cells when calculated per cartilage cell, and this value becomes progressively less with the age of the individual. Methylene blue raises the oxygen consumption ($Q_{O_2}^{M_b}$) of adult human costal cartilage by about twofold (Table I). However, it raises the oxygen consumption of cartilage from other species to as much as tenfold, suggesting that the cytochrome system is not as great a limiting factor for oxidation in human cartilage as in other species.

The rate of anaerobic glycolysis varies considerably with the age of the individual (Fig. 3). The anaerobic glycolysis of human costal cartilage at birth is +1.804, at 36 hours after birth it is +0.880, at 34 months +0.170, and beyond the age of 14 years it is +0.053. This same trend is observed in the sheep, cow, and chicken, although to a much lesser degree. It has been suggested that the decrease of anaerobic glycolysis is due to the decreasing cell count, and that the anaerobic glycolysis per cartilage cell remains constant. This appears also to be correct for human costal cartilage, since the anaerobic glycolysis decreases by about 90 per cent from birth to 70 years (Fig. 3), and the cell count decreases about the same during the same period of time (Fig. 2).

Since the potassium content of fetal human costal cartilage is 372.1 milliequivalents per kilogram dry, the cartilage loses about 90 per cent of this amount during 70 years of life, with most of the loss occurring within the first 14 years (Fig. 2). This correlates well both with the number of cartilage cells (Fig. 2) and the anaerobic glycolysis (Fig. 3). Thus, it would appear that not only does the anaerobic glycolysis per cartilage cell but also the potassium content remain constant throughout the life span. This observation has been made for bovine cartilage. The correlation of the potassium loss with the cell count is a reflection of the intra-

cellular position of potassium within the cartilage. If it is assumed that the majority of the potassium of cartilage exists intracellularly and that its concentration within the cell is about 140 milliequivalents per liter, then the volume of the intracellular water phase may be estimated by the method of Harrison and associates; intracellular water phase (c.c./kgm.) equals total potassium times 1000/140. The intracellular water phase was found to be 145 cubic centimeters per kilogram of fresh cartilage. Since the total water volume of fresh adult cartilage is 608 cubic centimeters per kilogram, the extracellular water volume, representing essentially an ultrafiltrate of blood plasma, is 463 cubic centimeters per kilogram of cartilage. The sodium concentration of the ultrafiltrate is about 144 milliequivalents per liter. Therefore, the extracellular water phase contains about 66.7 milliequivalents of diffusible sodium per liter. Since evidence exists that there is little sodium within the intracellular water, and since the total sodium is 172.46 milliequivalents per kilogram of fresh cartilage, it may be concluded that the remaining sodium is in the extracellular water phase in bound form. These values are in substantial agreement with those reported for other species.

The sodium content of human cartilage, when calculated on the basis of dry weight, exhibits a marked decrease with age. However, this loss of sodium is probably due to the loss of water which occurs with age since the sodium content calculated on a wet weight basis is relatively independent of age (Fig. 4). However, the loss of sodium is not in an iso-osmotic relation to the lost water since 36.0 milliequivalents of sodium are lost per kilogram of cartilage between the ages of 14 and 60 years, while only 102 cubic centimeters of water are lost per kilogram during this period. Thus, the removal of about 102 cubic centimeters of water could account for a deficit of 14.7 milliequivalents of sodium. Therefore, 21.3 milliequivalents of sodium were removed from the "bound" fraction of the extracellular water. It is not known whether this indicates an unbinding of sodium from this fraction (possibly being replaced by calcium), or an actual loss of both sodium and binding material itself with age. In any event, this observation would indicate a change in the quality or quantity of the chondroitin sulfate and not of the extracellular fiber proteins since they are not in a base-binding form.

SUMMARY

During the life span of man, cartilage exhibits a progressive loss of cells, and, as a result, the metabolic activity (e.g., respiration and anaerobic glycolysis) of the cartilage decreases proportionately. This loss of cells is also reflected in a decrease of potassium content. Further, a loss of sodium and water occurs involving a marked loss of sodium from the "bound" fraction of the extracellular space, indicating a change in the quality or quantity of the chondroitin sulfate-binding mechanism. This observation suggests a dependency of the extracellular material on the metabolic activity of the chondrocytes.

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THE PRODUCTION OF FAT EMBOLISM IN RABBITS BY FEEDING HIGH FAT MEALS

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THE AMOUNT of visible fat in the vascular system has been found to vary with the state of nutrition. The physiologic postprandial lipemias are an example. It has been noted by Weld in nontraumatized dogs and cats that the number of large stainable globules of fat in the blood vessels of the lungs increases after fat meals. After the fracture of one femur in rabbits, many more large fat globules appear in the lungs of fat rabbits than in those of lean ones. In humans, Zeithofer and Reiffenstuhl showed the incidence of fat embolism in routine postmortem examinations was far greater in periods of relatively good nutrition than in periods of poor nutrition.

Despite these observations we were surprised to find that fat emboli were probably a major cause of death in a group of rabbits fed single large fat meals. This observation stimulated the following study.

MATERIALS AND METHODS

Healthy albino rabbits weighing 2 to 4 kilograms were used. They were usually fasted 24 to 36 hours prior to the tube feeding. The feeding consisted either of cream or a vegetable oil. The largest feeding (8 gm. per kgm. body weight) contained a lipid concentration of 36 per cent. The smaller fat and oil feedings (0.5 to 4.0 gm. per kgm. body weight) were diluted with water so that the volume of the feeding was always the same. The fat feedings were introduced into the stomach by tube. Electrocardiographic standard 3 leads and bipolar electroencephalographic recordings were made simultaneously with a Grass electroencephalograph. Lipid determinations were made by extraction with ether-alcohol and weighing. Plasma proteins and lipoproteins were determined by paper electrophoresis using the Spinco Durum cell with *p*H 8.6 and 7.5 milliamperes for 16 hours. The plasma proteins were stained by bromphenol blue and lipoproteins by Sudan black B. Necropsy was performed on all animals at appropriate intervals or upon death, and their tissues were fixed in formalin. Later the tissues were stained by hematoxylin and eosin, and the Swank-Davenport (3) techniques. While blood samples were being taken from a marginal ear vein or electroencephalograms or electrocardiograms made, the animals were held prone in stocks which held the animals gently around the neck and around the body just forward of the hips.

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RESULTS

Mortality rate. Sixty-six rabbits were fed cream and 16 vegetable oil. The dose ranged from 0.5 to 8 grams per kilogram of body weight. Death did not occur in any animals receiving up to 4 grams per kilogram body weight of cream or oil. Twelve rabbits received 6.5 grams of cream or oil per kilogram of body weight. Forty-three per cent died 8 hours to 3 days after feeding (average length of life after feeding: 34 hours). Fourteen rabbits were fed 8 grams of cream or oil per kilogram of body weight. Fifty-seven per cent died 8 hours to 3 days later (average length of life: 20 hours). Only 5 animals received 6.5 or 8 grams of safflower oil per kilogram of body weight. The one on the higher dosage died. The animals which died

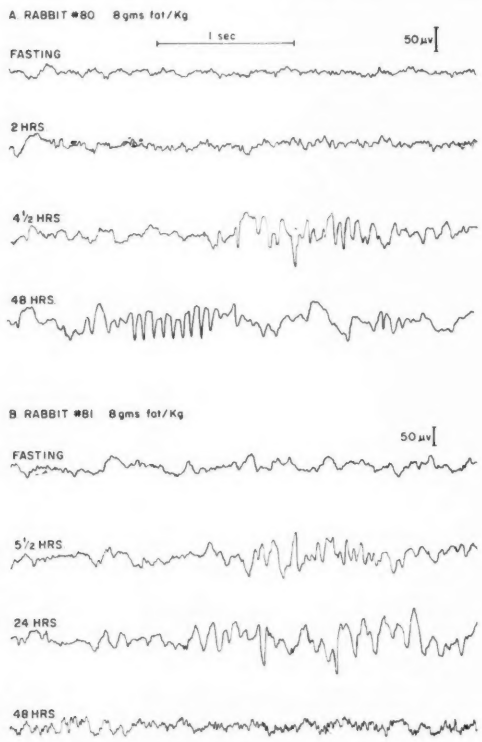

FIG. 1. Electroencephalographic changes in 2 rabbits after fat meals. A, Slow waves with periodic bursts of sharp waves 12 to 14 per second appeared at 4½ hours and remained until 48 hours after feeding. B, Similar abnormality is shown 5½ and 24 hours after fat feeding.

after fat feeding became progressively more quiet and weak, then cyanotic and dyspneic, and stuporous. Convulsions frequently occurred immediately before death.

Electroencephalograms. Satisfactory electroencephalographic studies were available in 34 rabbits. Significant changes were observed in 9 of the 16 animals that were fed 8 grams of lipid per kilogram of body weight, in 1 of 14 animals that were fed 2 grams of lipid per kilogram of body weight, and in 1 of the 4 animals fed 0.5 gram of lipid per kilogram of body weight. Electroencephalograms were normal in the 4 animals fed safflower oil. The remaining 30 animals received cream.

TABLE I.—TOTAL PLASMA LIPIDS (MGM. PER CENT) IN 14 RABBITS FED 8 GRAMS OF LIPID PER KILOGRAM OF BODY WEIGHT

	Control	*4 hours*	*11 hours*	*24 hours*
Average	233	244	245	293
Minimum	125	112	162	231
Maximum	412	356	356	500

The electroencephalographic changes consisted of generalized slowing and increased amplitude of the rhythmic electrical activity (Fig. 1A and B). These changes usually developed 4 to 8 hours after feeding and lasted for a period up to 48 or 96 hours. In some instances, periodic bursts of moderately high amplitude sharp waves with frequency of 12 to 14 per second were present (Fig. 1A, 48 hrs.). They occurred in an otherwise normal electroencephalogram, or in one in which diffuse slowing occurred. Bursts were similar to periodic burst activity in barbiturate narcosis.

Electrocardiograms. Satisfactory electrocardiographic studies were available in 34 rabbits. In 8 of the 16 animals that received 8 grams of oil or fat per kilogram of body weight, 3 of the 6 that received 4 grams of fat per kilogram, 4 of the 8 that received 2 grams of oil or fat per kilogram of body weight, and 1 of the 4 animals that received 0.5 gram of fat per kilogram of body weight, the electrocardiograms were abnormal. Three of these animals received safflower oil. In the only one that received 8 grams of safflower oil per kilogram of body weight, the electrocardiogram was abnormal.

Minor variations in the QRS complex and T waves were observed in unfed rabbits in which electrocardiograms were repeatedly done. These changes were insignificant compared with those observed after fat meals. Electrocardiographic changes which were considered abnormal appeared 4 to 8 hours after the fat meals and lasted for up to 72 or 96 hours. In 5 examinations after meals of 8 grams per kilogram of body weight, the electrocardiographic changes were marked. In all other instances (0.5 to 8 gm. per kgm. body weight) the electrocardiographic changes were moderate in degree and shorter in duration. Although

the *incidence* of electrocardiographic changes after 2 and 4 grams per kilogram of body weight of lipid was about the same as after 8 grams per kilogram body weight; abnormalities were less marked and shorter.

There were electrocardiographic changes in both the QRS complex and T waves, chiefly in leads 1 and 3 (Fig. 2). Changes were also noted in lead 2. In standard lead 1 the T waves often became exaggerated. In lead 3, T waves became inverted; concurrently the QRS complex became altered. These changes appeared 8 to 12 hours after fat meals and returned to or toward fasting pattern 72 or 96 hours later.

Lipid, lipoprotein, and blood urea nitrogen studies. The blood lipids were studied in 14 animals that received 8 grams of lipid per kilogram of body weight (Table I). The plasma lipids were increased 24 hours after feeding, although 4 and 11 hours after feeding very little change in plasma lipids had occurred. Electrophoretic studies demonstrated that lipoproteins stained by Sudan black B were either not changed or were decreased 4, 8, and 11 hours after the fat meals. They were significantly increased 24 hours after fat feeding. At no time was there more than a slightly visible lipemia, and this was maximum 24 hours after feeding.

Microscopic fat globules were demonstrated in dark field illumination in the urine from a number of rabbits after fat feedings. In 2 animals sacrificed 24 hours after fat feeding, urine from the bladder had a fat content of 435 and 188 milligrams per 100 milliliters. In others, abnormal amounts of protein were also found in the urine.

Because of the presence of albumin and of fat in the urine, blood urea nitrogens were determined at intervals up to 24 hours in 5 animals after receiving 8 grams of cream per kilogram of body weight, and in 3 animals after 8 grams of oil per kilogram of body weight. Prior to feeding, the urea nitrogens varied from 15 to 26 milligrams per 100 milliliters of blood. After feeding, the blood urea nitrogen was 30 milligrams per 100 milliliters or more in 4 of the 8 animals;

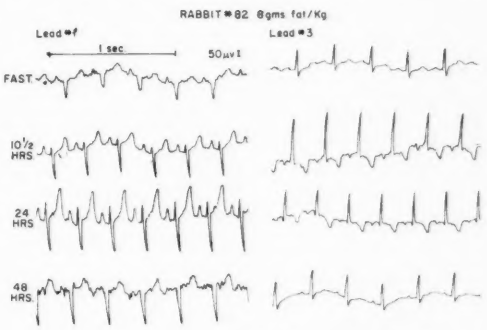

FIG. 2. Electrocardiographic changes in 1 rabbit in standard leads 1 and 3. Note increase in T wave and alteration in QRS complex 10½ and 24 hours after feeding in lead 1, and inversion of T waves at same time in lead 3.

45, 75, 60, and 30 milligrams per 100 milliliters, respectively.

Pathologic changes. The tissues of 25 rabbits were examined histologically. Fat emboli were demonstrated intravascularly in Swank and Davenport preparations (3). They varied in size from a few to approximately 100 microns in diameter and were most abundant in the blood vessels of the lungs (Fig. 3A, B and D), and kidneys (Fig. 3C). Less frequent emboli were seen in the blood vessels and perivascular spaces of the brain, heart, and liver. Multiple emboli were observed as early as 6 hours and as long as 96 hours after fat feeding. Visible pulmonary emboli were most numerous after tube feeding 2 and 4 grams of lipid per kilogram of body weight (present in 6 of 11 rabbits) and least numerous after feeding 6.5 and 8 grams of lipid per kilogram body weight (present in 1 of 14 rabbits). Fatty infiltration of the liver (Fig. 3G) was observed in but 3 cases, in each less than 48 hours after feeding, and fatty degeneration of the heart muscles (Fig. 3I) was observed in 8 animals.

Interesting changes were observed in the kidneys in animals that received 6.5 or 8 grams of lipid per kilogram body weight. About 4 to 6 hours after fat feeding, large amounts of lipid were observed in the proximal convoluted tubules in the cuboidal

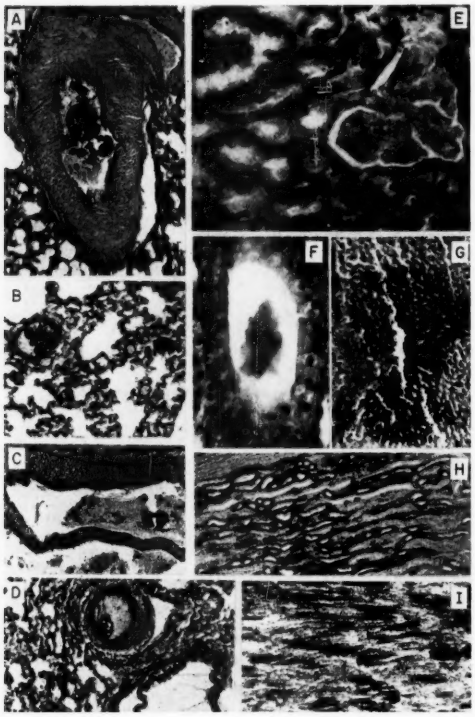

FIG. 3. Series of photomicrographs in fat fed rabbits (Swank and Davenport method counterstained by hematoxylin and eosin). A, Artery of lung filled with black-stained fat globules. B, Fat emboli in small arteries and capillaries of lung. C, Fat emboli in large artery in pelvis of kidney. D, Fat embolus in artery of lung. E, Fat globules in cuboidal cells of proximal convoluted tubules of kidney. Note also small fat globules in glomerulus. F, Fat globules in columnar epithelium of collecting tubules of kidney. G, Fatty infiltration in liver. H, Fat in distal convoluted tubules and loops of Henle in kidney. I, Fatty degeneration of heart muscle.

epithelial cells near their basement membranes (Fig. 3E). About 4 hours later the fat was observed similarly situated in the epithelial lining cells of the distal convoluted tubules (Fig. 3H), and in the loops of Henle. The proximal tubules at this time were relatively free of fat, and the endothelium of many proximal tubules had disappeared. Then, and a little later, fat appeared at the base of epithelial cells of some collecting tubules (Fig. 3F). Very small globules of fat were seen 4 to 8 hours after fat meals in some of the glomeruli (Fig. 3E).

DISCUSSION

The cause of death in our fat-fed rabbits was probably ischemia of the heart and brain due to inadequate circulation of the blood. This was suggested by the clinical symptoms leading up to death; by electrical changes in the electroencephalographic and electrocardiographic tracings (Figs. 1 and 2); and by histologic changes in the cardiac muscle (Fig. 3I). Two likely causes of impaired circulation are evident. First, Swank (4, 5) showed that after high fat meals adhesiveness and aggregation of the red blood cells, increase in the blood viscosity, and increase in the circulation time occur. Second, our histologic examinations revealed numerous unexpected fat emboli in the blood vessels of the lungs and elsewhere of our fat-fed rabbits. It is postulated that these two factors impeded circulation sufficiently to cause tissue hypoxia and death.

Our observations indicate that fat emboli were a critical factor in slowing the circulation only after the larger fat meals—in excess of 4 grams of lipid per kilogram of body weight. It is presumed that under these circumstances the ability of the blood to maintain the fat in a stable state of emulsion was exceeded, and that progressively larger and more numerous fat globules formed. Normally the lungs and systemic circulatory system are able to filter unknown, but probably significant, numbers of large fat globules from the active circulation. It would seem that this protective mechanism functioned in our animals, since many fat globules were found in the lungs of sacrificed animals that had received up to 4 grams of lipid per kilogram of body weight, and only a few had shown physical or pathophysiologic evidences of tissue hypoxia. After larger fat meals, greater histologic and physiologic evidences of tissue hypoxia were observed, yet fewer fat emboli were to be found in the lungs. It can only be assumed that the filtering capacity of the capillary bed had been exceeded; that numerous fat emboli had gotten into the general circulation; and that shock from

multiple microembolism of the brain, lung, and heart had resulted. The emboli were then washed into the general circulation, and massive cerebral and cardiac embolism resulted. Active removal of fat from the blood by the kidneys occurred but was probably ineffective after largest fat meals.

This interpretation of our histologic observations is supported by observations of Swank and Dugger (6). They showed that fat globules are to be found in the blood vessels of the lungs of rabbits. These globules were more numerous in fat than in lean rabbits. Following fracture of a femur there was a marked increase in the amount of fat in the lungs, but no increase of the fat in the brain. In fat rabbits the increase of lipid in the lungs after fracture was greater than in lean rabbits. Immediately after nembutal anesthesia there was a sharp increase in the number of fat globules in both the lungs and brains. If the animals had been fasted 24 hours prior to anesthesia, this change did not occur. It seems apparent that the capillary and precapillary bed of the lungs and systemic circulations acts as a filter and is capable of withholding large numbers of fat globules from the active circulation. During anesthesia the vascular system may relax, and in this case fat held in the capillary bed may be released into the general circulation and find its way to the brain. Since the brain is in a rigid sac (dura) which to some extent prevents effective vasodilatation, the free fat globules tend to become trapped in the brain.

The presence of large fat globules in the circulation in the absence of trauma of tissues and especially without large bone fractures suggests the blood itself as a major source of fat emboli. The visible fat in the blood is held in a state of emulsion. It is clear that the rabbit is poorly endowed to maintain a large amount of fat in this state. The absence of a heavy lipemia after very large fat meals indicates that either the fat was not absorbed, or that soon after absorption it came out of emulsion. The latter explanation appears indicated since so many large fat globules were found in the circulation, and so much fat was found in the nephrons of the kidney.

The distribution of fat in the kidneys is similar to the pattern of distribution of metachromasia noted by Austin in humans with metachromatic leucoencephalopathy (1), and in his animals after injections of compounds having a high negative charge (2). Our studies do not show whether fat arrives at different parts of the nephron unit from the glomerulus or directly from the capillary bed next to the basement membrane of the collecting and convoluted tubules.

SUMMARY AND CONCLUSIONS

Rabbits tolerate high fat feedings poorly, and many do not survive more than a few days. The cause of death appears to be tissue ischemia, presumably due to inadequate circulation. This fact is indicated by the behavior of the animals prior to death, by abnormal electrocardiograms and electroencephalograms several hours after fat feeding, and by tissue changes found postmortem. The cause of inadequate circulation is considered to be due, first, to adhesiveness and aggregation of red blood cells with slowing of circulation caused by high fat meals, and, second, to fat emboli found in many of our animals postmortem.

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INFLUENCE OF STAGED DIVISION OF MESENTERIC VESSELS UPON CIRCULATION TO ROUX-Y JEJUNAL LIMB

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In 1951, experimental studies were reported from this laboratory which demonstrated that staging the division of mesenteric vessels increases the length of intestine which can be mobilized with preservation of adequate circulation (3). This effect was observed both in rats and dogs, and in the latter animals, both with regard to the jejunum and the ileum. In most of the experiments, alternate branch mesenteric vessels were divided at the first operation and the intervening ones at a second procedure. In a few instances the same principle was tested with the construction of a Roux-Y limb, but most of them concerned the circulation to the intestine in continuity. This principle was applied clinically with success but has not been used for some years since we have come more and more to rely upon the right half of the colon for esophageal substitution.

The present experiments were devised in such a way that they were generally similar to, and yet somewhat different from, those previously reported. In these studies a Roux-Y anastomosis was constructed in all animals. Mesenteric vessels supplying the free end of the Roux-Y limb were divided at the first operation, and additional length was gained by later dividing more vessels.

MATERIALS AND METHODS

Experiments with rats. Domestic albino rats ranging in weight from 300 to 400 grams were used. They were anesthetized by the intraperitoneal administration of thiopental sodium. Operations were done with clean, but not sterile, technique. The abdomen was opened through an upper midline incision, and the jejunum and the ligament of Treitz were identified. The first mesenteric arterial branch and its accompanying vein situated just distal to the ligament of Treitz were preserved. The next 3 pairs of arteries and veins were divided and ligated at the root of the mesentery (Fig. 1). The jejunum was then sectioned at a point just distal to the area supplied by the first mesenteric artery, which had been left undisturbed, and an anastomosis of the proximal portion of the jejunum to a distal segment of the jejunum was made in such a way as to create a Roux-Y limb. The anastomosis was accomplished with a single layer of interrupted No. 6-0 silk sutures. The open end of the limb was then inverted and closed. In every instance there was evidence of persistent cyanosis of the distal end of the limb, and it was believed that division of another branch artery would have uniformly caused ischemic necrosis. The portion of the limb which was without direct blood supply was measured and the free limb of jejunum was then placed in a subcutaneous tunnel over the sternal area.

The animals were observed, and those which died were studied post mortem. The surviving animals were subjected to a second operation from 14 to 21 days after the first one. At this time the jejunal limb was further devascularized by division of the next most proximal branch mesenteric artery and accompanying vein. These ani-

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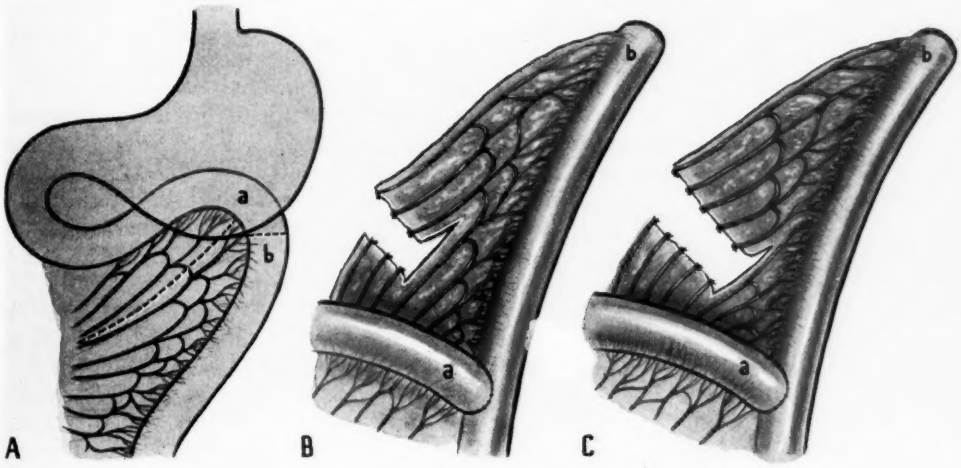

FIG. 1. Drawing illustrating the operative procedure carried out in both rats and dogs. A, The incision in the mesentery and the point of the division of the jejunum are illustrated. B, Division of the mesenteric arteries and construction of Roux-Y limb at the first operation. C, Division of additional mesenteric branch arteries at the second procedure.

mals were sacrificed from 7 to 10 days later, and the length of the jejunal limb not receiving direct arterial blood supply was again measured in the anesthetized animal just before it was sacrificed.

Experiments with dogs. Mongrel dogs ranging in weight from 8 to 12 kilograms were used. They were anesthetized by intravenously administered thiopental sodium. All operations were performed under aseptic conditions. The abdomen was opened through an upper midline incision. The jejunum and the ligament of Treitz were identified. The first branch mesenteric artery and vein to the jejunum just beyond the ligament of Treitz were left undisturbed. The jejunum was transected just distal to the point supplied by these first branch vessels, and an anastomosis of the proximal portion of the jejunum to the segment lower down was made so as to create a Roux-Y limb. The free end of the limb was devascularized by dividing between ligatures 2 or 3 of the mesenteric branch arteries and their accompanying veins. The vessels were ligated at the base of the mesentery. In each case the limb was rendered moderately ischemic as evidenced by continuing cyanosis, blanching, and increased contractions, and it was thought that any further loss of direct blood supply would have resulted in ischemic necrosis. The animals were observed carefully and postmortem examination was carried out upon those which expired. The surviving animals were subjected to a second operative procedure from 14 to 21 days after the first. At this time the length of the limb deprived of direct blood supply from the branch arteries was measured before and also after division of the next branch artery and its accompanying vein.

In an effort to reduce the intra-abdominal adhesions, a group of 5 animals was prepared in similar fashion except that the free limb of jejunum was placed inside a sterile cellophane tube. The tubing was not of adequate size, and all 5 animals expired within 3 to 7 days with gangrene and perforation of the limb, apparently as the result of venous obstruction. This group will be eliminated from further consideration.

A third group of animals was prepared in the same way except that the free limb of jejunum was placed in a covering tube of fine mesh nylon large enough so that it caused no venous congestion.

These animals were observed carefully, and postmortem examination was carried out upon those which expired. Those remaining were subjected to the same type of second stage operation as mentioned previously.

RESULTS

Results with rats. Thirty-eight animals were subjected to the initial operation. Twelve died within 1 week after this procedure. Ten (26 per cent) deaths were due to gangrene and perforation of the end of the jejunal limb. Two additional deaths resulted from intestinal obstruction at the site of the anastomosis. The devascularized segment of the jejunal limbs in the remaining 26 animals ranged in length from 3 to 7.25 centimeters and averaged 4.53 centimeters. All of the 26 animals survived the second operative procedure, and at the time of sacrifice the free jejunal limbs ranged in length from 4 to 10 centimeters and averaged 6.53 centimeters. Thus the staged division had resulted in an average increase in length of the free limb of 44 per cent. The circulation to the Roux-Y limb in all 26 animals remained excellent.

Results with dogs. In 30 dogs a jejunal Roux-Y limb was constructed, the branch arteries were divided, and no sheath or tube was placed about the jejunal limb. Eight (26.7 per cent) of the 30 died within a few days as a result of gangrene and perforation of the jejunum. One expired on the twentieth postoperative day, and no cause of death was evident on postmortem examination. Another died on the fourth postoperative day as the result of intestinal obstruction due to intussusception beyond the point of the jejunal anastomosis. In 10 animals the same initial operation was carried out except that the free jejunal limb was placed in a tubular sheath of fine nylon mesh. Three (30 per cent) of them died postoperatively of gangrene and perforation of the jejunum. The length of the free jejunal limb deprived of its direct mesenteric blood supply was measured both at the initial operation and again at the second operative procedure. The jejunal limb in the 27 animals surviving the initial operation ranged from 12 to 25 centimeters in length and averaged a trifle more than 15 centimeters. There was no measurable difference in the length of jejunal limb at the completion of the first operation and at the beginning of the second. At the second operation 2 of the 7 animals which survived the original procedure and the encasement of the jejunal limb in a nylon sheath were found to have necrosis of the tip of the jejunal limb without any peritoneal contamination. The necrotic tip was excised and the end closed again. Of the 27 dogs subjected to the second operation, 3 (11 per cent) died of gangrene and perforation of the intestine. The remaining 24 maintained excellent circulation to the free jejunum. The average length of the jejunal limb at the time the animal was anesthetized for sacrifice ranged from 17 to 30 centimeters and averaged 21.64 centimeters in length. Consequently the second procedure had resulted in an average increase in length of the free jejunal limb of 43 per cent.

DISCUSSION

The idea for the present experiments came from a conversation with C. W. Schwegman of Philadelphia who, after constructing a Roux-Y jejunal limb for esophageal replacement in a patient, found that it was of inadequate length. Temporary occlusion of another mesenteric branch artery brought about obvious ischemia. He left the jejunal limb as it was and at a second operation performed later he was able to divide additional branch arteries so as to provide adequate length with maintenance of excellent circulation. The jejunum was brought up retrosternally into the neck for anastomosis to the cervical esophagus.

Toward the completion of these experiments we learned of another similar clinical experience. J. Aylwin of Leeds, England, operated upon an 11 year old girl. Nine years previously an unsuccessful attempt at esophageal reconstruction had been made, necessitated by stenosis of a gastric mucosal lined esophagus. The original operator had fashioned a Roux-Y limb, removed approximately half of it because of inadequate circulation, and abandoned the effort. Aylwin found the original loop of jejunum to be somewhat atrophic but otherwise satisfactory. He divided two pairs of branch mesenteric vessels and obtained adequate length to carry out an anastomosis with the middle third of the thoracic esophagus, after amputating some of the atrophic end of the jejunal limb. At the time of exploration the first intact branch artery and vein supplying the jejunal limb were noted to be of considerably greater size than the remaining mesenteric branches.

Our experiments clearly demonstrate that the staged division of the branch mesenteric vessels to a Roux-Y jejunal limb does indeed increase the length of available jejunum by nearly 50 per cent both in rats and in dogs. At the same time, the staged division tends to provide excellent circulation. The experiments were so designed that the division of branch arteries was carried to a point where it resulted in obvious persistant cyanosis and ischemia of the tip of the jejunal limb. Obviously, one would not do this in a clinical case but it provided a very satisfactory test procedure in that at the initial operation the division of the branch arteries had been carried to its maximum or beyond it. In the case of the rat, after the initial operation 26 per cent of the animals died of gangrene and perforation of the jejunum, and there were no deaths following the second operation on 26 animals. In the case of dogs, death due to gangrene and perforation of the jejunum after the initial operation occurred in nearly 27 per cent of one group and 30 per cent of the other. In contrast, gangrene and perforation occurred in only 11 per cent of the 27 dogs subjected to the second operative procedure. At the time of the second operation, both in rats and dogs, the first remaining pair of vessels supplying the devascularized limb was noted to be increased in size as compared with the remainder of the branch mesenteric vessels. This same feature has also been observed by Aylwin in his patient.

These experimental results and the clinical cases of Schwegman and Aylwin suggest, therefore, that if a Roux-Y jejunal limb cannot be constructed in such a way as to provide adequate circulation to the free jejunum and length satisfactory for accomplishing the operative objective at the initial operation, additional length may be gained with preservation of adequate circulation by dividing further mesenteric branch vessels at a second operative procedure. This method would appear to be of considerable clinical usefulness under at least two different circumstances. The first concerns the case in which a jejunal limb of inadequate length has been constructed which cannot be made longer without impairment of the blood supply. This principle might also find usefulness when the plan has been to utilize the right half of the colon for esophageal reconstruction and an anomalous circulation with absence of the right colic artery is encountered.

Our experience as well as that of our associates suggest that when the blood supply to the right half of the colon is the usual one and when middle colic, right colic, and ileocolic arteries are present, adequate blood supply is almost sure to be maintained throughout the mobilized right half of the colon. The success of the procedure, however, seems to depend upon the presence of a right colic artery communicating freely through collaterals with the middle colic to the left and with the marginal vessels toward the cecum. When a right colic artery has not been present we have found that the mobilized right half of the colon has not maintained adequate circulation throughout its length. In such cases the

plan to use the colon should be abandoned and jejunum should be used instead, in a staged procedure if necessary.

SUMMARY

Experiments carried out in rats and in dogs demonstrated that the staged division of branch mesenteric vessels to a Roux-Y jejunal limb provided a mechanism for increasing the length of the free jejunal limb with preservation of adequate circulation. This principle would appear to have clinical usefulness.

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THE EFFECT OF PARTIAL EXTRACORPOREAL BYPASS ON SODIUM EXCRETION IN NORMAL DOGS AND IN THOSE WITH HEART FAILURE

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RECENT SUCCESS with total cardiopulmonary bypass for open heart surgery has stimulated interest in extracorporeal methods of assisting the failing heart. The four basic patterns of extracorporeal circulatory assistance, as shown by Harken, are: cardiopulmonary bypass, venoarterial shunt without oxygenator, selective ventricular bypass, and synchronized artificial ventricular assistance.

Cardiopulmonary bypass employing a mechanical pump in series with an oxygenator can be either partial or total. The latter method has been used and studied extensively for relatively short periods of time during open heart surgery. Therapeutic partial cardiopulmonary bypass in the patient with a failing heart and lungs has had only limited success. Evaluation of results during these attempts has been difficult because there was no objective and controlled index of improvement in these critically ill patients. This has led Harken and Dennis to discontinue attempts with partial bypass in human beings until the pathophysiology during and following assisted circulation in heart failure is more clearly understood. Further development and evaluation of methods and techniques in the laboratory animal, therefore, seemed indicated and prompted this study of the effects of partial cardiopulmonary bypass in heart failure. We have chosen to investigate this method of assistance in preference to the others because of its technical similarity with the well studied total bypass and because of its feasibility in the closed chest dog.

To assess the effect of assisted circulation on heart failure it is obviously necessary to have an animal with cardiac decompensation. Numerous methods for creating heart failure have been described in a previous article (8). The one based on the combined production of tricuspid insufficiency and pulmonary artery stenosis remains the most thoroughly studied. This method produces a reliable form of right-sided heart failure characterized by increased venous pressure, decreased exercise tolerance, loss of lean muscle mass, edema, ascites, and low fixed cardiac output. In animals with failure thus created, the urinary sodium excretion after a standard saline load has proved to be a reliable index of the degree of heart failure. Figure 1 illustrates the cumulative sodium excretion in a typical animal before and after the production of congestive failure by this technique. The marked change in sodium excretion with the onset of failure seemed to provide a potential method for evaluation of the effect of assisted circulation during partial bypass. Since the sodium retention after production of tricuspid insufficiency and pulmonic stenosis is nearly complete (Fig. 1), any improvement in the congestive failure might be expected to give a significant increase in the percentage of sodium load excreted.

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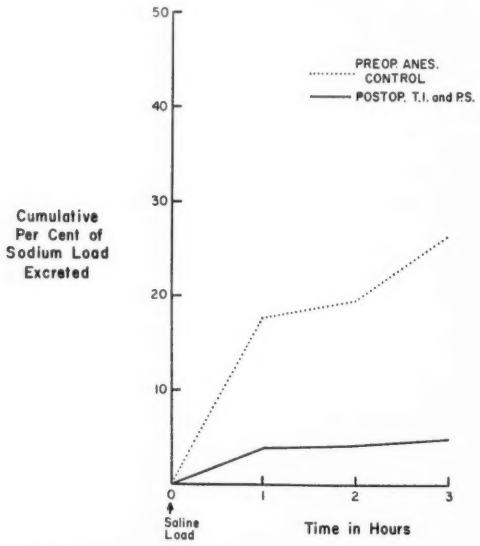

FIG. 1. Typical alteration in excretory response to a standard saline load following production of tricuspid insufficiency and pulmonary artery stenosis.

METHODS

Experiments were carried out on 20 apparently healthy mongrel dogs to create combined tricuspid insufficiency and pulmonary artery stenosis. Five died at or shortly after operation. In 15 animals heart failure was successfully produced. Four died of progressive chronic failure more than 6 weeks after operation but prior to bypass. Seven were used for other purposes. Four were assisted with partial bypass.

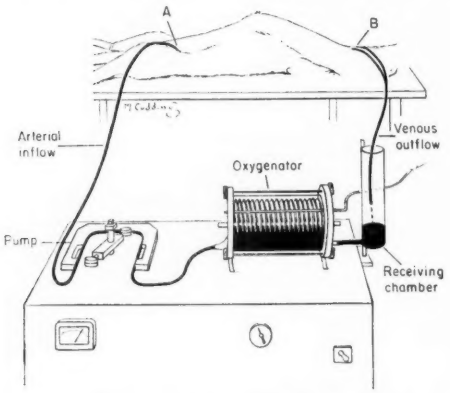

FIG. 2. Diagrammatic representation of system for partial bypass. Note that venous outflow is by gravity and that major serous cavities need not be entered.

Ten normal dogs were partially bypassed to perfect the technique of partial perfusion and to obtain control data. Light barbiturate anesthesia was used on all dogs. The scheme of assisting the circulation is shown in Figure 2. Two No. 30 French cannulas were passed through the external jugular veins into the right atrium or right ventricle for venous outflow. In 1 animal an additional catheter was introduced through the femoral vein into the inferior vena cava to increase the venous return. Cautery was used for all incisions to minimize bleeding. The arterial pressure was monitored through a plastic cannula, 1 millimeter in internal diameter, introduced through the carotid artery with its tip placed just distal to the aortic valve. Venous pressure was monitored by a 3 millimeter catheter in the inferior vena cava. In the heart failure animals a perineotomy was performed to facilitate the numerous catheterizations necessary for urine collection. The blood was drained by gravity into a reservoir, passed through a slightly modified Kay-Cross type of oxygenator and reintroduced by a De Bakey pump into the femoral artery. A 1,000 milliliter standard isotonic saline load was infused in less than 10 minutes within the 2 hour period before bypass. Prior to and during bypass, constant recordings were made of arterial and venous pressures, pulse and respiratory rate, and electrocardiogram. Urine specimens were collected at regular intervals for measurement of volume, sodium, potassium, and chloride. By measuring the oxygen consumption with a spirometer and sampling blood from the ascending aorta and the right ventricle, the cardiac output was calculated by the Fick principle. The flow across the oxygenator with its venoarterial difference was used to calculate the oxygen added and the carbon dioxide released in the extracorporeal system. Ten liters of oxygen per minute were passed through the 10 inch oxygenator which was

heated in an attempt to maintain the temperature of the blood at 37 degrees C. The discs were rotated at 100 revolutions per minute. The highest venous outflows were attained in the dogs with elevated venous pressures and when a third venous catheter in the inferior vena cava was used. The bypasses varied from 1 to 3 hours in duration.

OBSERVATIONS

Normal group. The response of a normal, trained, unanesthetized dog to a standard saline load has been studied extensively by Barger and associates (2, 3, 4). Since our perfusion experiments required general anesthesia, 2 normal animals were given a standard saline load under anesthesia for comparison. The sodium excretion rate was similar to that obtained in the conscious state (Fig. 3).

At the onset perfusions were technically unsatisfactory in some instances. However, in 7 of 10 animals constant bypass flow with stable arterial and venous pressures was achieved (Table I). The renal response to the saline load while on partial bypass fell within normal limits in 4 of these 7 animals (Fig. 4 and Table II). The chloride and water excretions were measured to be essentially the same as reported previously by Barger and associates but for simplicity are not presented here (3).

Heart failure group. The cumulative sodium excretion after a standard saline load was measured in 2 dogs on 3 occasions: before creation of heart failure, after its creation but prior to bypass, and during perfusion (Table III). In 2 dogs, only the preperfusion heart failure control was performed prior to measuring the response to the saline load while on bypass. The excretion curves of the same animals were then compared (Fig. 5).

In the failure animals that were perfused, technical problems did occur but satisfactory perfusions were performed in all (Table IV). While adjusting the flow and reservoir level at the beginning of perfusion

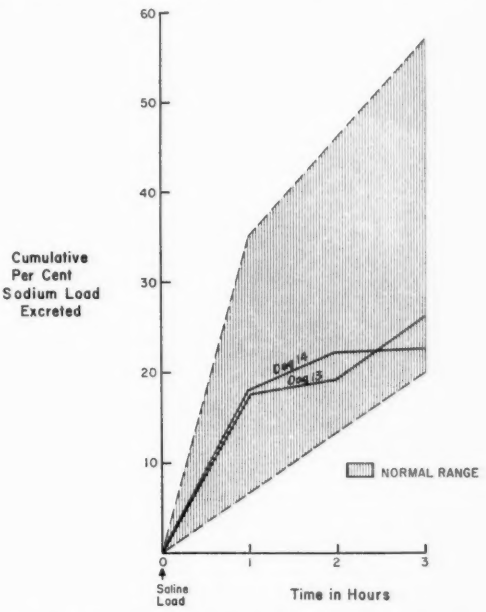

FIG. 3. Comparison of sodium excretion in response to standard saline load in normal anesthetized and normal unanesthetized dogs. Dashed lines define limits of normal for unanesthetized dogs as determined by Barger (3). Solid lines represent sodium excretion in 2 normal anesthetized dogs.

there was transient slight arterial hypotension but never for more than 1 minute. Only rarely and for short periods was the venous pressure reduced below the preperfusion level of 15 to 25 centimeters of saline. As expected, the venous pressure rose markedly when blood was added to the reservoir and an attempt was made to increase the arterial pump flow. Venous flow was increased to 2,800 milliliters in 1 animal without an increase in the venous pressure by the addition of a third catheter through the femoral vein into the inferior vena cava. If 1 of these 3 catheters was clamped, the venous outflow immediately decreased by one-third. It should be noted that during perfusion the sodium excretion was the same or less than the sodium excretion in the preperfusion control experiment despite the increase in total blood flow to the tissues (Fig. 5 and Table III).

TABLE I.—SUMMARY OF HEMODYNAMIC DATA IN 10 NORMAL DOGS PRIOR TO AND DURING BYPASS

Dog No.	*Weight, kgm.*	*Control cardiac output, ml.*	*Output of heart while on bypass, ml.*	*Average bypass flow, ml.*	*Per cent of circulation bypassed*	*Duration of bypass, mins.*	*Venous oxygen saturation on bypass, per cent*	*Survival*	*Comment*
1	17.0	—	—	400	—	127	—	Survived 2 months*	—
2	20.4	—	—	500	—	90	—	Died 2 hours*	Technical failure. Arterial pressure not maintained
3	25.8	—	—	1,000	—	135	—	Died 4 hours*	Technical failure. Arterial pressure not maintained
4	17.1	—	—	250	—	—	—	Died during bypass	Technical failure. Venous outflow poor and irregular
5	16.3	950	164	600	79	115	59	Died 8 hours*	Hypothermia occurred. Av. temp. 31° during bypass
6	11.5	—	—	550	—	120	—	Died 24 hours*	—
7	21.2	11,250 5,850	11,900 8,310	550 1,200	4.4 12.6	60 60	87 85	Survived 1 month*	High control cardiac output not fully explained. Hyperthermia occurred. Av. temp. 39.5° during bypass
8	17.8	2,450	1,600	500	24	150	78	Survived 3 weeks*	
9	19.6	2,230	2,020	650	24	55	76	Died 72 hours*	
10	22.2	3,980 3,020	3,270 2,480	750 1,200	19 33	45 20	66 58	Survived 3 weeks*	

*Time after bypass. All survivors sacrificed at times indicated.

TABLE II.—SODIUM EXCRETION IN RESPONSE TO STANDARD SALINE LOAD IN NORMAL DOGS PRIOR TO AND DURING BYPASS

Dog No.	*Sodium load, mEq.*	*Water load, ml.*	*Na control, per cent of sodium load excreted*	*Duration of collection of Na control, mins.*	*Bypass begun*	*Na_1, per cent of sodium load excreted*	*Na_2, per cent of sodium load excreted*	*Bypass flows, ml., during collection of— Na_1*	*Na_2*
1	78	500	8.2	60		20.3	12	400	400
2	156	1000	Technical	Failure		No urine	Excreted	500	500
3	156	1000	Technical	Failure		No urine	Excreted	1000	1000
4	156	1000	Technical	Failure		No urine	Excreted	250	100
5	156	1000	41.8	160		0.6	—	600	—
6	156	1000	31.6	60		2.77	2.08	550	550
7	156	1000	8.7	60		11.1	13.6	550	1200
8	156	1000	34.4	113		7.8	1.1	500	500
9	156	1000	28.8	145		1.2	0.8 (40 mins.)	650	650
10	156	1000	19.9	120		1.9 (45 mins.)	1.0 (20 mins.)	750	1200

Na control = sodium excretion in period prior to bypass; Na_1 = sodium excretion in first period during bypass; Na_2 = sodium excretion in second period during bypass. All periods are 1 hour unless otherwise indicated.

All of the animals in the heart failure group responded to painful stimulation following perfusion but none survived more than a few hours. At autopsy the gross findings were consistent with severe heart failure as described previously by Barger and associates (1). In addition there was marked increase in the ascites and peripheral edema as compared to the preperfusion state.

In contrast, 4 of the 7 normal dogs that had technically satisfactory partial bypasses survived.

DISCUSSION

Although normal sodium excretion has been obtained with total bypass in the normal dog perfused for short periods of time, we are not aware of similar studies with

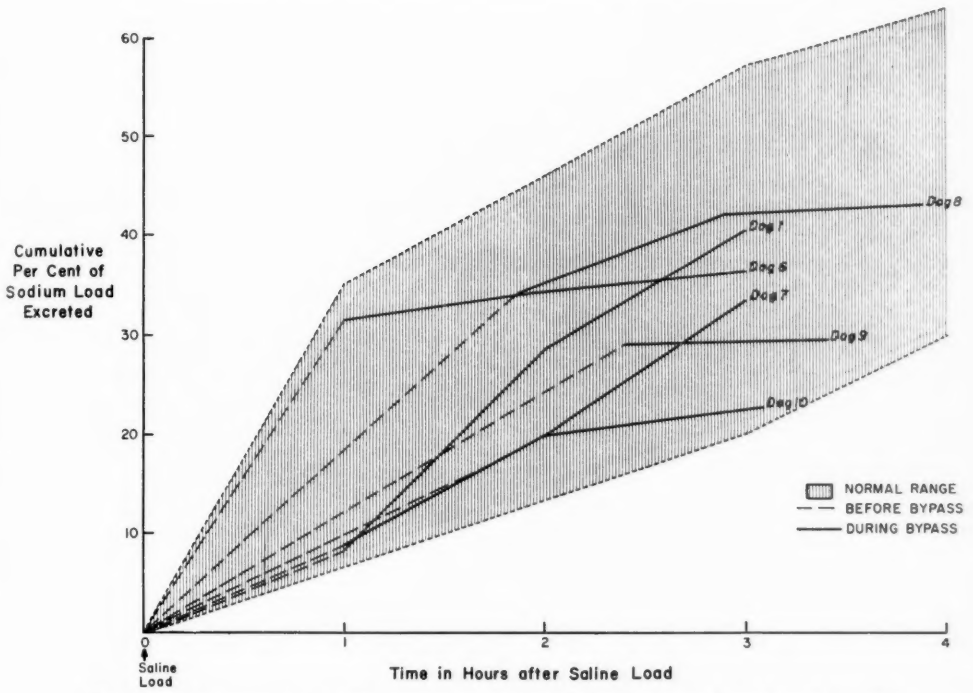

FIG. 4. Sodium excretion in response to a standard saline load in normal anesthetized animals before and while on bypass. Dashed lines indicate sodium excretion prior to bypass. Solid lines indicate sodium excretion while on bypass. Shaded area indicates normal range of excretory response in unanesthetized animals as determined by Barger (3).

partial bypass in either the normal or heart failure dog.

In the normal animal, partial bypass per se does not seem to change remarkably the renal response to a standard saline load (Fig. 4). This response is significant because it shows that, while on bypass with the technique used in this experiment, an essentially normal sodium diuresis can be expected in the normal animal. Furthermore these data, by showing that bypass alone need not affect sodium excretion, serve as a control for comparison with the heart failure group during bypass. These control data support the use of sodium excretion as an index of the circulatory status during bypass in the heart failure animal. Aside from the numerous potential pitfalls such as air embolus, hemolysis, transient hypotension, and hypothermia that are associated with all bypass techniques, no explanation can be offered for the subnormal renal response to the saline load in the 3 remaining dogs satisfactorily perfused.

The bypass was relatively small in all the normal animals and accounted for approximately 25 per cent of the total blood flow except in 1 animal in which hypothermia occurred inadvertently. In this dog the bypass measured only 600 milliliters but accounted for 80 per cent of the total blood flow to the tissues. This is far below the normothermic cardiac output for this animal which would be approximately 2,000 milliliters per minute. Despite this low tissue perfusion the metabolic needs were probably satisfied as evidenced by the high venous oxygen saturation (Table I). This observation suggests a possible means of attaining a relatively large percentage of

TABLE III.—SODIUM EXCRETIONS IN 4 DOGS AFTER ADMINISTRATION OF STANDARD SALINE LOADS

Dog No.	Weight, kgm.	Standard sodium load, mEq.	Standard H_2 load, ml.	A Per cent Na_1	A Per cent Na_2	A Per cent Na_3	A Per cent Na Total	B Per cent Na_1	B Per cent Na_2	B Per cent Na_3	B Per cent Na Total	C Per cent Na_1	C Per cent Na_2	C Per cent Na_3	C Per cent Na Total
11	12.	156	1000	—	—	—	—	.46	.57	1.24	2.3	.15	.1	—	.25
12	16.7	156	1000	—	—	—	—	.14	.07	.07	0.28	0.0	0.0	—	0.0
13	19.5	156	1000	17.4	1.8	7.0	26.2	3.5	.6	.18	4.3	3.86	0.0	—	3.86
14	16.4	156	1000	16.5	5.8	0.44	22.7	4.86	.95	.4	6.2	1.5	0.0	—	1.5

A, Prior to creation of heart failure. *B*, After creation of heart failure without bypass. *C*, After creation of heart failure with bypass. Na_1, Na_2, and Na_3 refer to per cent of sodium load excreted in the first, second, and third hours after sodium loading respectively.

TABLE IV.—SUMMARY OF HEMODYNAMIC DATA IN 4 HEART FAILURE DOGS PRIOR TO AND DURING BYPASS

Dog No.	Weight kgm.	Control cardiac output, ml.	Output of heart while on bypass, ml.	Average bypass flow, ml.	Per cent of circulation by-passed	Duration of bypass, mins.	Venous oxygen saturation on bypass, per cent	Survival, hours after bypass completed	Comment
11	12.2		—	750	—	130	—	0	Arterial pressure poorly maintained. Died during bypass
12	16.7	2240	890	1000	53	60	57	4	
13	19.5	3300	1520	1200	44	75	54	6	
14	16.4	1440	935	2800	75	83	68	2	Extra venous cannula used to obtain high flow

bypass with a low actual pump flow. In other words, using hypothermia, 80 per cent of the work of the heart could be taken over by the extracorporeal apparatus at pump flows equal to 20 per cent of the normothermic cardiac output.

Attempts to increase the venous outflow in the normal dogs by adding blood to the reservoir were not successful and did not result in an increased venous pressure. This supports the observation of Herron and associates that an increment in the blood volume on bypass is accommodated in the vascular bed in normal animals.

In the heart failure animals we were unable to demonstrate an increase in sodium excretion during partial bypass. However, this negative response may be due to factors other than the failure of partial bypass to provide circulatory assistance.

For instance, an elevated venous pressure itself may be a factor in the sodium retention in heart failure. In the animals in failure the venous pressure was elevated initially and, despite all attempts to augment outflow, was never lowered during bypass. This observation is difficult to explain but may be related to the free tricuspid insufficiency, tight pulmonary stenosis, and high resistance provided by the relatively limited cross-sectional area of the venous cannulas relative to the venae cavae. An open chest preparation with total bypass may be necessary in order to permit the use of large venous cannulas to increase the outflow and decrease the venous pressure. This would help to unravel the cause of sodium retention in a known type of congestive heart failure that has been studied extensively from other points of view. However, it certainly is not a practical form of assisting failing human hearts.

Recent work has suggested that increased sympathetic tone may also be a factor in sodium retention. It is theorized that in heart failure a reduced cardiac output results in a decreased stimulation of the carotid sinus which in turn initiates increased sympathetic tone resulting in sodium and water retention. Although partial bypass elevates the arterial blood pressure and should thereby decrease carotid-sinus-induced sympathetic tone, other mechanisms of initiating sympathetic overactivity

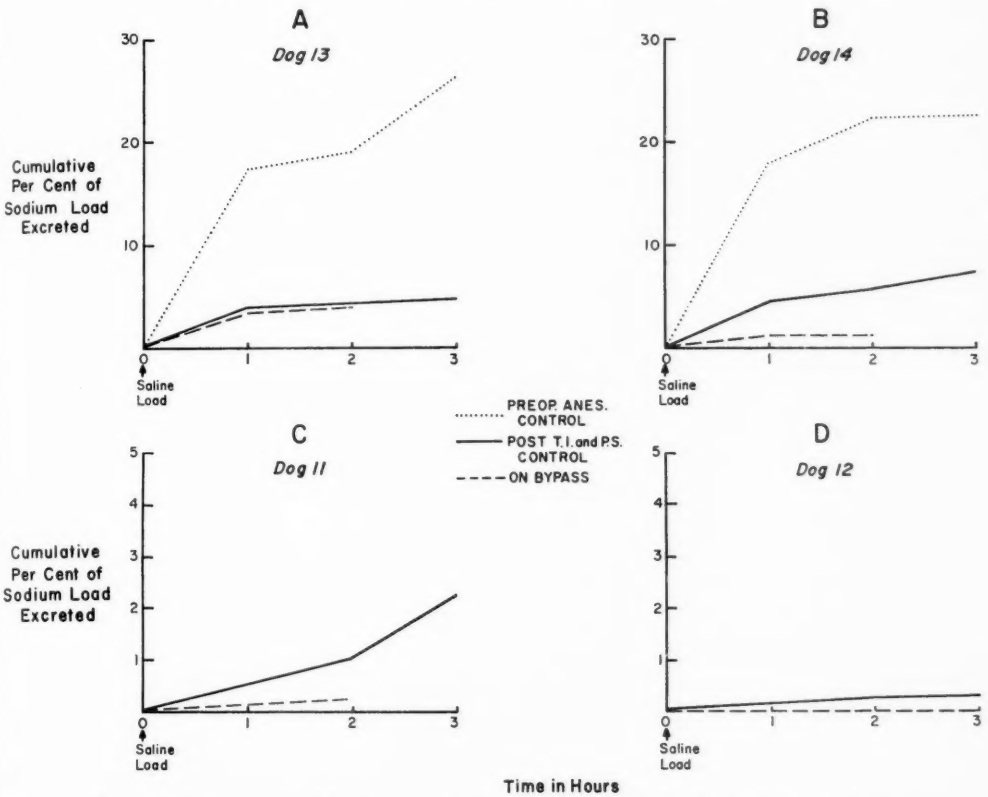

FIG. 5. Sodium excretion following a standard saline load: A, In a single dog before production of heart failure (dotted line), after its production (solid line), and after its production while on bypass (dashed line). B, The same in a second dog. C, In a single dog after production of heart failure (solid line) and after its production while on bypass (dashed line). D, The same in a second dog.

may exist and be unaffected by partial bypass assistance in spite of its increased total body perfusion. It must be pointed out also that this study was confined to a particular form of right-sided heart failure and that the results might be quite different in other forms of cardiac failure.

Another possible mechanism to explain the failure of sodium excretion to increase in the face of augmented tissue perfusion is suggested by a recent study of heart failure animals showing hypertrophy of the zona glomerulosa of the adrenal cortex. The mechanism of water and sodium retention in heart failure may be influenced by endocrine factors, notably aldosterone. These factors might well not be influenced by short term partial bypass, and consequently no increase in the sodium excretion could be expected.

Furthermore, it is entirely possible that the technical problems associated with the perfusion, such as transient hypotension and anoxia, could account for the lack of improvement in the sodium excretion. On the other hand, these factors did not seem to interfere with sodium excretion in 4 of the 7 normal dogs that were satisfactorily perfused.

A final possible explanation for the failure of partial bypass to provide circulatory assistance is the antagonism between the

action of the mechanical pump and the heart which could theoretically exist. Synchronized ventricular assistance would be necessary to overcome this difficulty.

Although the sodium excretion as an index of the degree of failure is further substantiated by parts of this study, it was impossible to demonstrate any significant change in the sodium excretion rate during bypass in the heart failure animals. However, it is still possible that partial perfusion in its present form is not adequately evaluated by using sodium excretion as a measure of the circulatory status. Nevertheless, the failure of these animals to improve as evidenced by an increase in pulmonary congestion, hepatic congestion, ascites, and peripheral edema with death supports not only the sodium excretion as an index of circulatory status but also the clinical impression that partial bypass in its present form does not benefit heart failure.

SUMMARY AND CONCLUSIONS

1. Partial extracorporeal heart-lung bypass has been performed in normal and heart failure dogs.

2. Satisfactory partial bypass has been achieved in 7 of 10 normal animals. In 4 of the 7, while on partial bypass, the sodium excretion in response to a saline load fell within normal limits.

3. In the heart failure animals, sodium excretion, while on partial bypass, was the same or less than the excretion during the control run without bypass.

4. Although the majority of the normal animals which were successfully bypassed lived, all of the failure animals died shortly after perfusion with obvious further congestive changes.

5. Further animal investigation is indicated before applying partial perfusion in its present form to the heart failure patient.

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EXPERIMENTAL BRAIN INJURY AND DELAYED HYPOTHERMIA

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PREVIOUS STUDIES (5) demonstrated that hypothermia affected profoundly the pathologic character and mortality of acute experimental brain injury. If the body temperature was 25 degrees C. or less at the time of injury, the resulting lesion was partially hemorrhagic, evoking only mild posttraumatic edema and little or no leucocytic response. This was in contrast to normothermic conditions, under which a wedge-shaped, markedly hemorrhagic lesion was found which was followed by a severe, progressively inflammatory reaction in the form of cerebral edema and local leucocytic infiltration. In addition, the size of injury was established which would be 50 per cent lethal at normal body temperature. When the same sized lesion was produced during hypothermia, the mortality rate was only 1 in 15 (7).

If protection is afforded by a reduction of body temperature at the time of injury, can benefit be expected when hypothermia is induced following a normothermic brain injury? This would be the equivalent of treating brain injuries by the use of hypothermia. The presently reported experiments were undertaken to answer this question.

METHODS

Mongrel dogs, weighing between 10.0 and 15.0 kilograms and unselected as to age and sex, were used in this investigation. At the start of each chronic experiment the animal was given 600,000 units of long-acting benzathine penicillin G intramuscularly. Diphenylhydantoin sodium, 0.4 gram daily, was given orally to suppress convulsions; this was continued through the fifth posttraumatic day in surviving animals.

Anesthesia was achieved with intravenous pentobarbital sodium, 30 milligrams per kilogram, and the dogs were intubated with a cuffed No. 38 Fr. endotracheal catheter. The catheter was attached to an automatic positive-negative pressure closed-system respirator which delivered 100 per cent oxygen at a rate of 24 respirations per minute. The positive pressure was adjusted between 7 and 11 millimeters of mercury and the negative pressure was set between 1 and 4 millimeters of mercury in order to maintain a tidal exchange of 200 to 400 milliliters. A thermistor was inserted 200 millimeters into the esophagus for the recording of body temperature. The animals which were to receive brain injuries at normal body temperature were maintained in the 35 to 39 degree C. range with the aid of a heating pad when necessary. Hypothermia was induced by immersion to the shoulders in ice water. Rewarming was accomplished by immersion in a water bath in which the temperature was maintained 10 degrees C. higher than body temperature until normothermic levels were attained.

Standardized brain injuries were produced by application of liquid nitrogen in a brass cylinder to the surgically exposed dura mater and subjacent brain. Details of the method have been described elsewhere (5). Pressure measurements were made with a standard water manometer connected to a No. 19 gauge needle in the cisterna magna.

All animals were sacrificed with an overdose of sodium pentobarbital. The brains were removed and fixed in 10 per cent iso-

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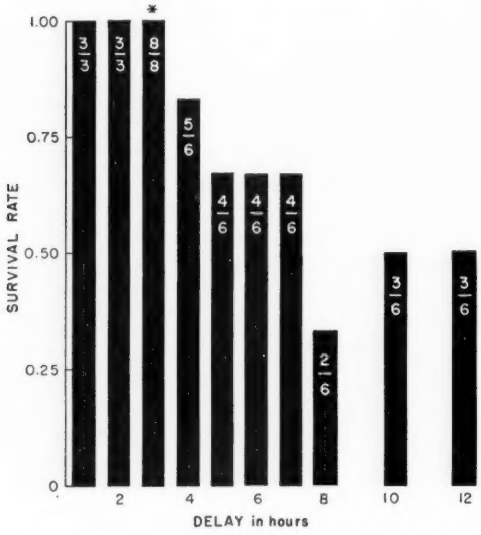

FIG. 1. Delay of the induction of hypothermia plotted against survival rate.

tonic sodium acetate formalin. The volume of the lesion was determined by the technique described previously (5). Random sections were taken for histologic examination.

RESULTS

Determination of the normothermic median lethal sized injury. Lesions were produced in 49 normothermic dogs. Injuries of different magnitudes were created by varying the contact time between the liquid nitrogen application and the dura mater and subjacent brain. The contact time ranged between 0 and 10 minutes; the size of the lesions ranged between 0.3 and 9.0 milliliters. The results were arrayed into 9 groups, and the mortality rates of the groups were calculated as their probits. The number killed, expressed in probits, was plotted against the size of the lesion in milliliters. Analysis of the probit regression line yielded a median lethal injury (LD_{50}) of 5.42 milliliters. This sized lesion was found to correspond to a contact time of 3½ minutes.

Having established that a 5.42 milliliter lesion could be expected to kill 50 per cent of normothermic dogs, this sized injury ±2 standard errors was created in a group of hypothermic dogs. The lesions were produced when the body temperature was 25 degrees C. or less, and the dogs were maintained at this temperature for 1 hour. They were then rewarmed and observed for 7 days. Under these conditions, 14 of 15 hypothermic dogs survived. This is a mortality rate of 1 in 15 and is significantly different from that of the normothermic dogs ($p<0.01$). However, the most important question was still unanswered: what was the effect of hypothermia on brain injury, if the temperature was reduced after the injury had occurred at normal body temperature?

Brain injury followed by hypothermia. Standard LD_{50} sized lesions were produced in 10 groups of dogs under sodium pentobarbital anesthesia at normal body temperature. At variable times after injury, ranging from 1 to 12 hours, the induction of hypothermia was begun and the body temperature was reduced to 25 degrees C. or less. Cooling was accomplished in 75 to 90 minutes. The temperature was maintained at this level for 1 hour only, and then the animals were rewarmed, taking 80 to 100 minutes to return to normal body temperature. They were observed for 7 days and sacrificed with an overdose of sodium pentobarbital. All brains were removed, fixed, and sectioned 7 days later, at which time the size of the lesion was determined. Only animals with lesions measuring 5.42 milliliters ±2 standard errors were included in this study. The survival rate of each group was plotted against the delay time for induction of hypothermia (Fig. 1).

It may be seen that all animals survived in which the induction of hypothermia was begun within 3 hours after injury, the first death occurring after 4 hours' delay. The 3 hour delay group was therefore enlarged until 8 of 8 dogs had survived. At this point, it was determined that this survival rate was probably significantly different from that of the normothermic controls ($p<0.05$).

The study was continued past the 3 hour delay mark until the survival rate returned

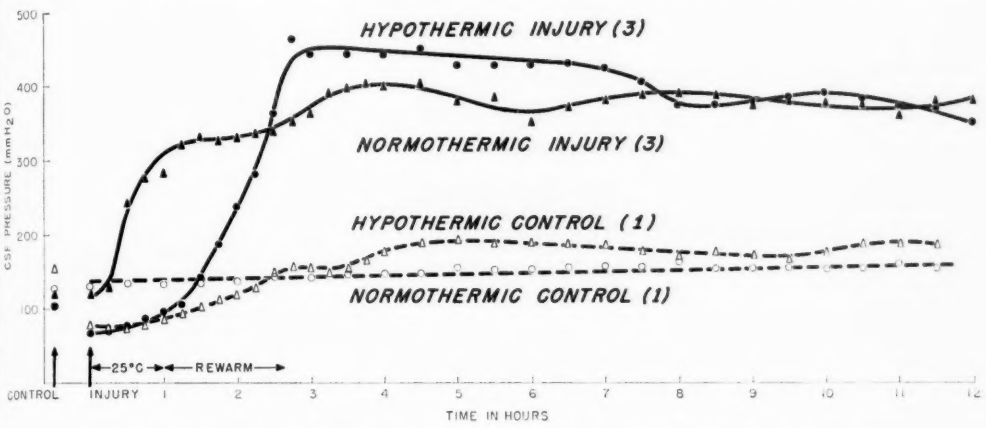

FIG. 2. Cerebrospinal fluid pressures at normal body temperature and during hypothermia, with and without standard brain injuries.

to the previously established 50 per cent level for this sized lesion. This point was reached after between 7 and 8 hours' delay. However, between 3 hours and 7 to 8 hours' delay, survival was greater than 50 per cent, 5 of 6 at the fourth hour, and 4 of 6 at the fifth, sixth, and seventh hours. This observation suggests that there may be partial protection if hypothermia is induced during this interim period, but the numbers of animals tested in these groups were not large enough to establish statistical significance.

Cerebrospinal fluid pressures following brain injury at normal body temperature and during hypothermia. A series of experiments were performed in which the cerebrospinal fluid (CSF) pressures of normothermic and hypothermic dogs, with and without injuries, were measured. The CSF pressures of several dogs were measured on a water manometer connected to a No. 19 gauge needle inserted into the cisterna magna. Readings were taken every 5 to 10 minutes during a 12 hour period following the establishment of equilibrium.

The CSF pressures were observed during 12 hours of controlled normothermic conditions and during 1 hour of hypothermia at 25 degrees C. followed by rewarming to normal body temperature (Fig. 2). No injuries were produced in these animals, but they were anesthetized throughout the experiment with sodium pentobarbital. It may be seen that there was little change in the CSF pressure during a 12 hour period at normal body temperature. The hypothermic control showed a decrease in CSF pressure from 155 millimeters of water at normal body temperature to 78 millimeters at 25 degrees C. With rewarming, the pressure returned to the precooling level and remained stable thereafter over a 12 hour period. There was no "rebound" rise in pressure after the return to normal body temperature. Next, the average CSF pressures of 3 dogs with LD_{50} sized brain injuries at normal body temperature were plotted (Fig. 2). These animals were anesthetized but breathing spontaneously during the experiment. Within the first hour after injury, there was a precipitous rise in pressure from 120 to 300 millimeters of water. Thereafter, the pressure slowly increased to a peak of 400 millimeters between the third and the fourth hours and remained stable thence through the twelfth hour of observation.

The average CSF pressures of 3 dogs with brain injuries produced at a body temperature of 25 degrees C. were also plotted against time. During the 1 hour of hypothermia, there was a small rise in pressure following injury, 68 to 97 millimeters of

water. With rewarming and return to normal body temperature, the CSF pressure at the third hour increased to a somewhat higher peak than the normothermic-injured animals. By the seventh to eighth hour, both normothermic and hypothermic pressures equalized and remained stable thereafter.

Cerebrospinal fluid pressure and delayed hypothermia. The question arose of the course of CSF dynamics during delayed hypothermia following brain injury. Cerebrospinal fluid pressures were measured in 3 dogs. The induction of hypothermia was begun 3 hours after the occurrence of the standard brain injury at normal body temperature, the same conditions under which previously all chronic animals had survived.

The normothermic-injury CSF pressure curve was plotted simultaneously with the average 3 hour delay hypothermia CSF pressures (Fig. 3). As had been seen in Figure 2, there was an immediate rise in pressure within the first hour after injury. Thereafter, the pressure increased gradually, approaching the peak by 3 hours. At this point, hypothermia was induced. The slight downward trend just before the 3 hour mark coincided with the commencement of artificial respiration and hyperventilation preparatory to the immersion in ice water. As the body temperature fell, the CSF pressure also decreased, in keeping with the reported data of Rosomoff and Gilbert, Lundberg and Neilsen, and Lemmen and Davis. At 25 degrees C. the pressure had fallen to 165 millimeters of water from 375 millimeters of water just prior to cooling. However, with rewarming following the 1 hour of hypothermia, the CSF pressure rose once again to precooling heights, paralleling the pressure of the animals which had not been subjected to hypothermia. Except for the decline of pressure during cooling, there had been no detectable effect on CSF pressure during the 12 hours of observation. It would have been interesting to know the level of CSF pressure later in the posttraumatic course of events; unfortunately, these pressures were not obtained. It is possible that an alteration in the CSF pressure levels may have been seen had the period of observation been prolonged.

DISCUSSION

In the first study of this series (5), it was clearly demonstrated that the maintenance of a reduced body temperature did change the pathologic character of this type of experimental brain injury. Hypothermia prevented the development of the progressive, fulminating edema associated with such injuries at normal body temperature. Hypothermia also aborted the posttraumatic inflammatory cellular response. Despite these seemingly beneficial effects, when the animals were rewarmed, they all eventually died, albeit survival time was 5 times longer than the normothermic controls. In a similar type study, Raimondi and his co-workers confirmed these findings; their survival times were extended 9 times the control value without affecting mortality. However, in both groups of experiments, lesions were utilized whose size was so large as to be uniformly fatal in all animals. No attempt was made to establish or utilize a minimal lethal dose.

From the data of the present experiments, it is possible to show that many of the lesions exceeded appreciably the minimal lethal dose. With such large lesions, there would be little chance of demonstrating a significant therapeutic effect without utilizing large numbers of animals. Therefore, we came to believe that the conclusions of our earlier experiments and those of Raimondi and his co-workers were not tenable because of the small numbers studied relative to the size of the injury produced. Hence, the problem was re-evaluated by employing the concept of the median lethal dose or LD_{50}. The LD_{50} concept is one in which the lethal effect is determined from a single application in a small group of animals. When the LD_{50} is compared with results of another dosage schedule or method of treatment, the difference in response and its significance may be evaluated by the method of Burns.

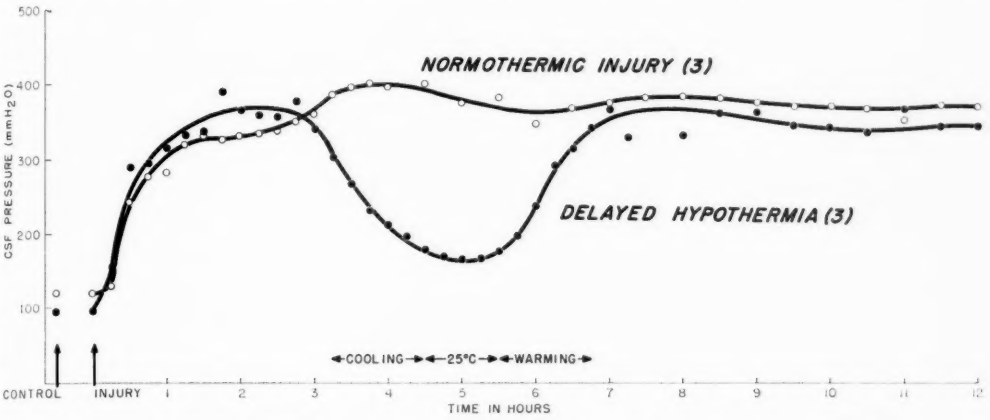

FIG. 3. Cerebrospinal fluid pressure after brain injury at normal body temperature and with delayed hypothermia.

The use of this technique did result in the demonstration that hypothermia affects the mortality of acute brain injury.

If these data are to be transposed to the management of clinical head injuries, it is conceded that hypothermia may not alter greatly the mortality rate of the very severely injured, even though the survival time may be lengthened. However, the group of patients who are less severely injured, the LD_{50} class, should benefit dramatically from the use of hypothermia. Clinical data are still too sparse for evaluation, although the preliminary results suggest that hypothermia is effective, especially in the latter group.

There appear to be two pertinent observations and discrepancies resulting from these studies. The first disparity is between the level of CSF pressure and brain volume. During the first hour after injury, there is a precipitous increase in brain volume and CSF pressure; here, the two functions act in tandem. Thereafter, the brain volume continues to increase progressively until at the end of 12 hours, the volume is almost double that seen after 1 hour (5). By contrast, the CSF pressure rises slowly after the first hour to a peak by the fourth hour, remaining relatively stable thereafter up to 12 hours. Thus, the CSF pressure measurements do not reflect the continuing sizable increase in brain volume, i.e., cerebral edema, which occurs between the fourth and twelfth hour.

The second discrepancy is between the level of CSF pressure and mortality. Under the conditions of this study, there appears to be no correlation between the two. It is true that during the induction and maintenance of hypothermia, the CSF pressure was reduced. Yet, with rewarming, the pressures reverted to the levels established for the normothermic controls, seemingly affected only temporarily by the reduction in temperature. Despite this, mortality was drastically reduced coincident to the application of hypothermia. This fact suggests that CSF pressure is not one of the indices from which the prognosis relative to mortality may be deduced. In fact, under conditions of these experiments, it would seem that CSF pressure measurements during the first 12 hours after injury are of little value either in estimating the degree of cerebral edema or the rate of survival.

This study demonstrated that hypothermia did afford protection against the mortality of a standard acute brain injury. The mechanism by which this was accomplished was not revealed by the experimental design. Examination of the tissues suggested that the inflammatory reaction to injury

had been modified by the cooling process at the cellular level. Definition of the responsible mechanism will require the use of techniques more refined than those under present consideration. The results of these experiments certainly justify further study, especially in the direction of more fundamental forms of investigation.

SUMMARY AND CONCLUSIONS

The size of brain injury was established which would kill 50 per cent of animals at normal body temperature. The same sized lesion was produced in dogs at a body temperature of 25 degrees C. After 1 hour of hypothermia, they were rewarmed and observed for 7 days. The dogs which were cooled had a mortality rate of 1 in 15. Cerebrospinal fluid pressure measurements during the first 12 hours after injury indicated that CSF pressures remained lowered during hypothermia, but with rewarming to normal body temperature, the pressures increased to the same level as that of the normothermic animals.

LD_{50} lesions were produced in groups of hypothermic dogs. At variable times after injury, ranging from 1 to 12 hours, hypothermia was induced, maintained for 1 hour, and the animals were rewarmed. If hypothermia was begun within 3 hours after injury no deaths resulted after rewarming. If the delay was longer than 7 to 8 hours after injury, no protection from hypothermia was found, and the mortality rate once more reverted to 50 per cent. CSF pressure measurements under these circumstances indicated a temporary decrease in pressure during hypothermia. After rewarming, CSF pressures paralleled the normothermic-injured values.

It was concluded that: (1) hypothermia protects against the mortality of experimental brain injury if the temperature is reduced sufficiently early after injury; (2) cerebrospinal fluid pressure measurements fail to demonstrate a correlation between the degree of cerebral edema and mortality.

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FURTHER EXPERIENCE WITH BIOFLAVONOID COMPOUNDS IN RH IMMUNIZED WOMEN

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In 1956, a preliminary report dealing with the use of bioflavonoid compounds in Rh immunized mothers was published (1). Much has been written on the effect of bioflavonoid compounds on prevention of capillary fragility, and it is fairly well accepted that the mechanism of Rh iso-immunization is based on the concept that Rh positive fetal cells enter the maternal circulation through a "break" in the placental capillary system. Many investigators have shown with various techniques that, in normal pregnancy, varying degrees of capillary placental "breaks" occur with decidual bleeding and escape of fetal cells into the maternal circulation. If these capillary "breaks" could be eliminated or reduced, thus eliminating or reducing the transfer of Rh positive cells into the circulation of an Rh negative mother, the degree of iso-immunization might possibly be minimized. In Rh negative mothers previously immunized by Rh positive blood transfusions or pregnancy, further iso-immunization might be prevented. Rh antibodies are small and freely cross the placenta, hence antibodies already present would not be affected, but if further transfer of fetal cells could be prevented, further degree of iso-immunization might be forestalled. Six cases were presented in an attempt to illustrate this point, but 6 isolated cases prove very little.

It is believed that if a comparison of Rh negative mothers given bioflavonoids throughout their pregnancy could be made with a similar group not given bioflavonoids but otherwise handled identically, i.e., preterm delivery if feasible and early exchange transfusion to the newborn infant, more evidence as to the value of this drug could be ascertained.

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MATERIALS AND METHODS

Seventy-one Rh negative mothers immunized by either pregnancy or blood transfusion with Rh positive blood, i.e., having delivered one or more erythroblastotic infants or having received a transfusion with Rh positive blood and having demonstrated Rh antibodies in the nonpregnant state, were studied during a given pregnancy which resulted in an Rh positive baby. The final outcome in this group was compared with that in a group of 32 Rh negative mothers similarly immunized, but having received bioflavonoids in the form of CVP capsules of from 400 to 600 milligrams daily, beginning early in pregnancy and continuing until delivery. The two groups were otherwise managed identically—preterm delivery if feasible and prompt exchange transfusion to the newborn.

RESULTS

Group 1 consisted of mothers who had delivered 1 or more infants with mild to moderate erythroblastosis but survived, or mothers who had been immunized with Rh positive blood but had had no previous pregnancy.

Thirty-two such patients in the nonbioflavonoid group were observed. One infant was a hydropic stillborn; 9 were severely jaundiced and anemic and died in the immediate neonatal period in spite of attempts at exchange transfusion. Twenty-two were moderately affected, were given one or more exchange transfusions, and survived.

The survival rate was 22 of 32, or 68.8 per cent.

Sixteen such patients in the bioflavonoid group were observed. One infant was severely affected (hydrops) and died shortly after birth. Fifteen were moderately affected and all survived after exchange transfusion. The survival rate was 15 of 16, or 93.7 per cent.

Group 2 consisted of mothers who had delivered 1 or more live-born infants who died in the neonatal period in spite of all attempts at therapy.

Twenty-four such patients in the nonbioflavonoid group were observed. Seven infants were hydropic stillborn and 17 died in the immediate neonatal period. None survived in this group.

Six such patients in the bioflavonoid group were observed. One infant was a hydropic stillborn; 2 died in the immediate neonatal period; 3 survived after 1 or more exchange transfusions. The survival rate was 3 of 6, or 50 per cent.

Group 3 consisted of mothers who had delivered 1 or more previous stillborn infants.

Fifteen such patients in the nonbioflavonoid group were observed. All 15 delivered hydropic stillborn infants.

Ten such patients in the bioflavonoid group were observed. Two infants were hydropic stillborn. Two died almost immediately after birth. Six infants survived after 1 or more exchange transfusions. The survival rate was 6 of 10, or 60 per cent.

SUMMARY

A total of 71 patients in the nonbioflavonoid group produced a total of 22 surviving infants, or 30.9 per cent, whereas a total of 32 patients in the bioflavonoid group produced a total of 24 surviving infants, or 75 per cent.

Offhand, these results would seem striking but it must be admitted that the bioflavonoid group is small by comparison and that larger numbers of patients must be treated before more definite conclusions can be reached. Such studies are in progress and future reports will be forthcoming.

REFERENCE

1. Jacobs, W. M. Use of bioflavonoid compounds in the prevention or reduction in severity of erythroblastosis fetalis. Surg. Gyn. Obst., 1956, 102: 233.

HEALING OF BRONCHIAL WOUNDS FOLLOWING PULMONARY RESECTION

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LAYER-TO-LAYER approximation of epithelium and other tissue layers in wounds of the skin and other organs has been found to provide optimal anatomic conditions for healing. In bronchial closures, however, it has often been the practice to suture the walls with the epithelium brought together surface against surface. This method of bronchial closure would seem theoretically improper because there is lack of approximation of the tissue layers deep to the mucosa, and one might expect a tendency for the parallel epithelial layers to grow outwardly instead of together. This circumstance should invite delayed wound healing with an increased tendency of wound leakage, resulting in an increased incidence of infection with abscess and fistula formation.

Bronchopleural fistula is still a much feared complication following pulmonary resections, but before the antibiotic era it caused a more alarming incidence of fatalities. At that time a method of bronchial stump closure, as shown in Figure 1, with epithelial surface approximation became and has remained the most popular method, possibly because it is technically easier. Friedrich and Halsted realized the fallacies of this method of closure and attempted to remove the mucosa of the distal bronchial walls so as not to have epithelial surface against epithelial surface; they had little success because of the firm adherence of the mucosa to the underlying tissue. Meyers and Crafoord effected closure by invaginating the distal ends in a manner similar to methods practiced in gastrointestinal surgery. Brewer advocated a technique which utilized the membranous portion of the bronchial wall as a flap. Bjork (3) and Gibbon recently have demonstrated techniques of pneumonectomy in which the bronchus is amputated at the trachea, followed by anatomic layer-to-layer approximation of the cut edges.

Heuer and Dunn were the first to demonstrate the microscopic appearance of healed bronchial stumps. Rienhoff and associates in their report of experimental bronchial closures showed that healing occurs at the cut ends. They stressed the importance of reinforcing the bronchial wound with extrabronchial tissue. Various methods of closures are well summarized by several authors. Methods of both Sweet (similar to group I, Fig. 1) and of Overholt (similar to group II, Fig. 2) have been widely practiced.

In 1941, Condon reported a study of epithelial regeneration in bronchi of white rats. He found that regenerating epithelium is first squamous in type and becomes columnar and ciliated as healing progresses. He also found that the growth and quality of the epithelium reflect the quality of the underlying stroma. Epithelial regeneration in bronchi has also been studied by Adams, Taffel, Ferguson, Kiriluk, and their associates.

This study was undertaken to evaluate the importance of the principle of layer-to-layer approximation in the healing of bronchial wound closures. This investigation, in contrast to most previous studies of bronchial healing which have stressed healing of the outer fibrous cap, emphasizes healing of the mucosa and its underlying stroma.

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Supported by the Surgery Development Fund.

The survival rate was 22 of 32, or 68.8 per cent.

Sixteen such patients in the bioflavonoid group were observed. One infant was severely affected (hydrops) and died shortly after birth. Fifteen were moderately affected and all survived after exchange transfusion. The survival rate was 15 of 16, or 93.7 per cent.

Group 2 consisted of mothers who had delivered 1 or more live-born infants who died in the neonatal period in spite of all attempts at therapy.

Twenty-four such patients in the nonbioflavonoid group were observed. Seven infants were hydropic stillborn and 17 died in the immediate neonatal period. None survived in this group.

Six such patients in the bioflavonoid group were observed. One infant was a hydropic stillborn; 2 died in the immediate neonatal period; 3 survived after 1 or more exchange transfusions. The survival rate was 3 of 6, or 50 per cent.

Group 3 consisted of mothers who had delivered 1 or more previous stillborn infants.

Fifteen such patients in the nonbioflavonoid group were observed. All 15 delivered hydropic stillborn infants.

Ten such patients in the bioflavonoid group were observed. Two infants were hydropic stillborn. Two died almost immediately after birth. Six infants survived after 1 or more exchange transfusions. The survival rate was 6 of 10, or 60 per cent.

SUMMARY

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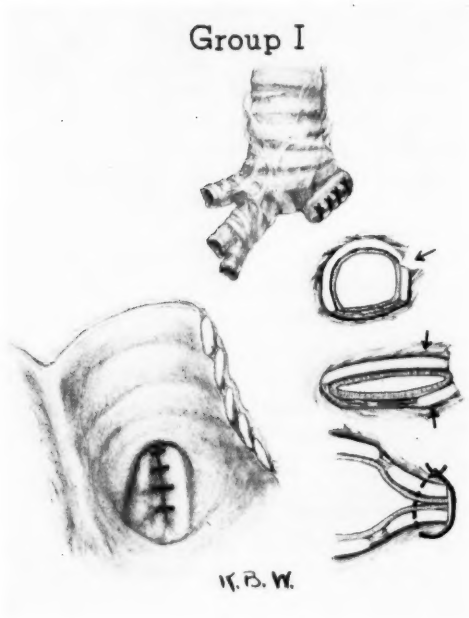

FIG. 1.

vein were ligated and sectioned individually, and the peribronchial tissue was carefully dissected away from the bronchus just proximal to the tracheobronchial junction. The larger superior bronchial lymph node was excised to decrease the amount of tissue overlying the bronchial wounds. In some cases the mucosa was removed from the underlying tissue by chemical cauterization; mechanical methods proved too traumatic. For this, 100 per cent phenol, 10 per cent trichloracetic acid, or sticks of 40 per cent silver nitrate were used and followed by saline irrigation. Suture material on atraumatic needles was used to close the bronchi.

Three methods of closure were employed (Table I). In group I (Fig. 1), amputations were performed leaving about 5 millimeters of bronchial stump. Incisions across 1 or 2 bronchial cartilage rings were made to facilitate collapse. The walls were sutured with epithelial surface approximation with about 5 interrupted No. 3–0 sutures through all layers of the cut ends. In 7 of these 16 closures the distal mucosa was chemically cauterized prior to suture.

In group II (Fig. 2) the bronchi were amputated so as to leave 5 to 10 millimeters of bronchial stump. Midway on the bronchial stumps, between the bronchial ends and the tracheobronchial junction, 3 or 4 No. 4–0 chromic catgut mattress sutures were placed, surrounding 1 cartilage ring, to approximate opposite walls. In 5 of these 8 closures the mucosa lying distal to the mattress sutures was chemically cauterized. The distal

METHOD

Left pneumonectomies were performed by aseptic technique on 40 mongrel dogs weighing between 9.0 and 16.6 kilograms. Intravenous pentobarbital, 30 milligrams per kilogram, preceded by 8 milligrams of morphine and 0.5 milligram of atropine, was given for anesthesia. An intermittent positive pressure automatic respirator was used. The approach was through the bed of the fourth rib. The pulmonary artery and

TABLE I.—METHODS OF BRONCHIAL CLOSURES

Group		*I*		*II*		*III*			
						A			*B*
Type of approximation		Epithelial surface		Epithelial surface		Layer			Layer
Type of tension-relieving sutures		None		Proximal catgut sutures		None			End catgut sutures
Chemical cauterization of mucosa		−	+	−	+	−			−
Type of material for end sutures		Silk	Silk	Silk	Silk	Silk	Gut	Nylon	Silk
No. days postop. when examined	7 or less	7*	6*	1	4*	2	1*	1	7*
	14	1	1	2†	1	1	1	1	1
	28	1	0	0	0	0	0	0	1

*Represents 1 postoperative death.
†Represents 1 empyema without bronchopleural fistula.

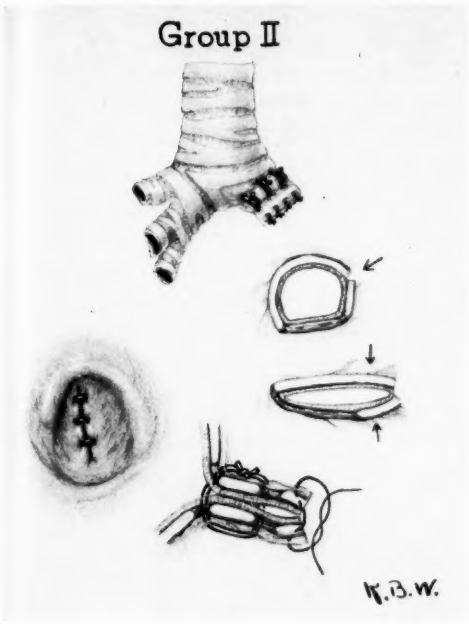

FIG. 2.

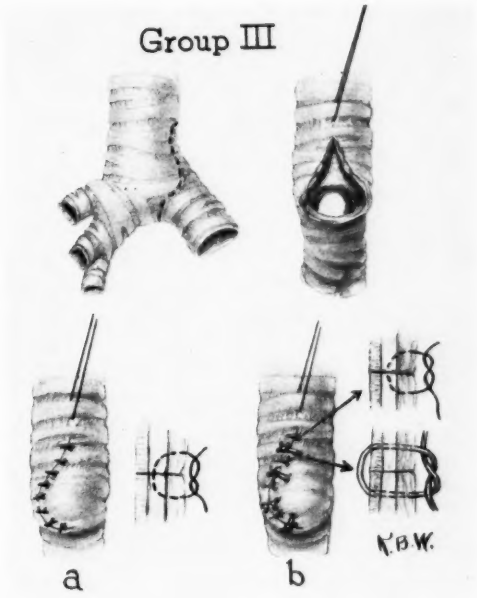

FIG. 3.

walls were approximated surface-to-surface with interrupted No. 3–0 silk sutures which were placed through all layers of the bronchial ends except the mucosa.

In group III (Fig. 3) the bronchi were amputated at the tracheobronchial junction where a V-shaped portion of tracheal wall which extended through the 3 tracheal rings lying superior to the bronchus was removed. Inferiorly, the amputation was carried circumferentially through the proximal portion of the first bronchial ring. In 6 of these 15 closures (Fig. 3a) either No. 3–0 silk, No. 4–0 chromic catgut, or No. 6–0 nylon interrupted sutures were used to approximate the cut walls in a layer-to-layer fashion with an attempt to remain extramucosally. In the remaining 9 closures (Fig. 3b), the distal bronchial walls were approximated layer-to-layer with catgut and No. 3–0 silk interrupted sutures. Approximately 4 catgut sutures were placed without any particular attempt to avoid penetrating the mucosa, and about 5 silk sutures were then placed extramucosally. Like tissue layers on opposite cut bronchial ends were approximated in their proper planes by means of this type of amputation and suturing. As suggested by Gibbon, a traction suture was placed proximally in each trachea of this group prior to amputation. This provided good access to the operative site and it also eliminated the technical difficulties of a short amputation.

None of the bronchial wounds in this experimental study were covered or reinforced with extrabronchial tissue. A proximal noncrushing blood vessel clamp was applied gently in some of the closures in each group, during which time bleeding still occurred from the membranous walls. If leaks from the sutured bronchi were present when tested under saline, 1 or 2 additional sutures were added to make them airtight. The remaining right lung was then well expanded as the chest wall was closed. Penicillin and streptomycin were given for 2 days postoperatively.

TABLE II.—RESULTS OF HEALING

Dog No.	Closure method*	Postop. day examined	Defects at closure site: cyst: Pouch	cyst:	Sinus	Sutures protruding into lumen: Silk	Gut	Types of epithelial coverage†: squamous: Absent	squamous:	Columnar	Quality of epithelium‡	Quality of subepithelial tissue§
21	I	7	+	−	+	2	−	f	f	+	++	++
24	I	7	+	−	+	3	−	f	+	−	+	+
33	I	7	+	−	+	3	−	−	f	+	++	+
41	I	7	+	−	+	4	−	−	f	+	+++	++
52	I	7	+	−	−	3	−	f	+	−	+	+
54	I	7	+	−	+	3	−	−	+	−	++	+
27	I	14	+	−	−	2	−	−	f	+	+++	+++
79	I	28	+	−	+	2	−	f	−	+	+++	++
20	I°	7	+	−	−	3	−	f	+	−	+	+
22	I°	7	+	−	−	1	−	−	+	f	++	+
31	I°	7	+	−	−	3	−	f	+	−	+	+
47	I°	7	+	−	−	5	−	f	+	f	++	++
51	I°	7	+	−	−	1	−	f	+	−	+	+
29	I°	4#	+	−	(fistula)	4	−	+	f	f	+	+
26	I°	14	+	−	−	5	−	f	f	+	++	+
55	II	7	+	−	+	0	2	−	f	+	+++	+++
56	II	14	+	+	−	0	2	−	f	+	+++	+++
57	II	14	+	+	−	0	2	−	f	+	+++	+++
13	II°	7	−	−	+	0	1	−	f	+	++	++
17	II°	7	+	−	−	0	3	−	+	−	+	++
61	II°	5#	−	−	(fistula)	0	2	+	+	f	++	+
64	II°	7	−	−	+	0	2	f	f	+	++	++
12	II°	14	+	−	+	1	1	f	−	+	++	++
63	IIIA	7	−	−	−	0	0	−	−	+	++++	+++
68	IIIA	7	−	−	−	1	0	−	−	+	++++	+++
71	IIIA	14	−	−	−	0	0	f	−	+	+++	+++
69	IIIA	1#	−	−	−	−	4	+	f	−	+	++
70	IIIA	14	−	−	−	−	3	−	−	+	++++	+++
83	IIIA	7	−	−	−	(3 nylon)	−	−	−	+	++++	+++
62	IIIB	7	−	−	−	0	3	−	−	+	++++	+++
67	IIIB	7	−	−	−	0	3	−	−	+	++++	+++
73	IIIB	7	−	−	−	0	2	−	−	+	+++	+++
80	IIIB	7	−	−	−	0	1	−	−	+	+++	+++
81	IIIB	7	−	−	−	0	1	−	−	+	+++	+++
82	IIIB	1#	−	−	−	0	2	+	f	−	+	++
84	IIIB	7	−	−	−	0	1	−	−	+	+++	+++
78	IIIB	14	−	−	−	0	0	−	−	+	++++	+++
72	IIIB	28	−	−	−	0	0	−	−	+	+++	+++

*See Table I.
†The type of epithelial coverage (absent, squamous, or columnar) is indicated by the following: (+) present, (−) not present, or (f) focally present.
‡The quality of the epithelium was graded according to the amount of differentiation from a low thin squamous layer to tall thick columnar layer of epithelium with cilia and goblet cells.
§The subepithelial layer refers to the stroma which is located superficial to the cartilage layer. Retention of inflammatory and necrotic products and edema were considered unfavorable.
° Bronchial mucosa chemically cauterized.
#Postoperative deaths.

The dogs were sacrificed 7 to 28 days after operation (Table I), and the intact wounds were examined grossly. After excision and fixation in 10 per cent formalin, multiple cuts were made across the wounds perpendicular to the suture line. From 1 to 8 areas of each specimen were stained with hematoxylin and eosin for microscopic study.

The wounds were observed for the presence of pouches, cysts, sinuses, and fistulas. The number of sutures protruding into the lumen of epithelial coverage was determined by the thickness of the epithelium and by the amount of cell differentiation. The presence of cilia and goblet cells implied a high degree of differentiation. The quality of the stroma lying superficial to the cartilage layer was evaluated for the amount of inflammatory reaction, and necrotic material was also noted.

Pressure studies were done on the first 12 animals by removing the tracheobronchial tree and excising the excessive tissue overlying bronchial wounds. With the right main bronchus occluded, air pressure was applied through the trachea. Pressure was

increased until leaking and bursting at the wound site occurred. Because of errors caused by overlying mediastinal and peribronchial tissue, the results were unreliable and the pressure testing was discontinued.

RESULTS

Results are tabulated in Table II. Five postoperative and 1 anesthetic death occurred. One death in group I was due to excessive cauterization which caused a bronchopleural fistula. One death in group II was due to a retained sponge which caused a bronchopleural fistula. One death in group I and 2 deaths in group III were from undetermined causes, possibly cardiac in origin. In 2 additional dogs empyemas not involving the bronchial stump developed, presumably from surgical contamination. Thirty-four dogs were in good condition during their entire postoperative period. In all cases there was obliteration of the left pleural cavity by mediastinal shift and the chest wall was well healed. The average weight loss was 0.9 kilogram.

In group I (Fig. 1) closures, with epithelial surface approximation, there were from 1 to 5 silk sutures extending into the inner bronchial lumen (Fig. 4). Surrounding these sutures was redundant granulation tissue much of which was uncovered with epithelium (Fig. 5). A conspicuous inflammatory process (Fig. 6) was frequently demonstrated along the suture material which communicated with the lumen. Near and beyond these sutures were shallow sinuses. The thickness and differentiation of the epithelium were from poor to fair. The subepithelial layer in group I closures showed edema and rather extensive inflammatory reaction and necrotic material. In the cauterized bronchi, necrosis in the subepithelial stroma was prominent, and thin, poorly differentiated epithelium was usually found. Bronchial stump pouches were consistently found in these closures.

In group II (Fig. 2) closures, using end silk sutures with proximal catgut mattress sutures, no silk sutures protruded into the lumen. There was reaction about the proximal catgut mattress sutures when they still existed. At the distal suture line there was a fairly thick columnar epithelium and the subepithelial stroma was without much inflammation or necrosis (Fig. 7). In 2 cases, however, pouches and cysts were present between the proximal catgut sutures and the distal silk sutures (Fig. 8). In the cauterized bronchi, necrosis and inflammation were more prominent (Fig. 9).

FIG. 4. Two silk sutures protruding into the bronchial lumen of dog 79 (group I) 28 days after operation. This closure was done with epithelial surface approximation.

In group III (Fig. 3) closures, with layer-to-layer approximation, excellent healing was usually noted without pouch or cyst formation. There was advanced epithelial regeneration manifested by a thick layer of differentiating columnar epithelium with cilia and goblet cells even near the center of the suture line (Fig. 10). The stroma of the subepithelial layer usually contained only a minimum of inflammatory and necrotic material and contained frequent bronchial glands. There were no silk sutures visible within the lumen of the bronchi in which tension-relieving catgut sutures were utilized. Epithelial coverage was complete except in small areas where occasional remains of catgut suture were still present. In the group III closures using only end silk sutures, occasional silk sutures could be viewed from inside the lumen. These su-

FIG. 5. Redundant granulation tissue in the bronchial lumen overlying the silk suture material of a group I closure.

FIG. 6. A sinus extending out from the bronchial lumen to a silk suture which is a nidus for infection in a group I closure.

tures, however, were often covered by epithelium and protruded much less frequently than in group I closures. Catgut sutures which extended into the lumen appeared to have less adjacent reaction than silk sutures which extended into the lumen. The monofilamented nylon sutures had very little surrounding reaction.

The results of healing in the bronchial closures done with layer-to-layer approximation (group III) were superior to those closures done with epithelial surface approximation (group I).

DISCUSSION

Good bronchial healing will lessen incidence of postoperative tension pneumothorax and bronchopleural fistulization and should reduce the incidence of chronic localized complication. Roll has reported frequent intraluminal ulcerations in bronchial stumps following pulmonary resection for tuberculosis. Bjork (3) has indicated the frequent necessity of removing silk sutures by bronchoscopy from bronchi after bronchial closure. With the performance of plastic reconstructive procedures on bronchi, less catastrophic complications consisting of chronic localized infection, ulceration, and suture granulomas with stricture formation have become of particular concern.

Certain characteristics of the bronchus make it prone to poor wound healing. It is a semirigid and very mobile organ in which repairs must be airtight. There is a paucity of soft tissue in the bronchial wall and scarcely any adjacent tissue for support. Because pulmonary resections are accompanied by bacterial contamination, the wound is endangered by infection which is the greatest cause of bronchial fistulas.

There are differences in bronchial closure and healing in dogs as compared with human beings. Besides being free of infection these experimental dogs have smaller bronchi, more abundant peribronchial tissue, and more mobile mediastinums. Despite these differences, similarity of local factors

FIG. 7. Good healing in some areas of a group II type of closure. See Figure 8.

FIG. 8. An area of cyst formation in a group II type of closure.

exists. In this study efforts were made to standardize the procedures so that the quality of healing, with and without layer-to-layer approximation, could be evaluated.

One of the primary functions of bronchial epithelium is protection of its underlying supporting tissues. If epithelial coverage is not complete, irritating substances or infection may disrupt the process of fibrin formation. Once an adequately healing stroma is formed which can support an epithelial layer, the epithelium in turn acts as a bridge for ingrowth of granulation tissue. Epithelial regeneration is dependent upon the nutritional scaffold beneath it. The growth and character of epithelium reflects the quality of the underlying stroma and is therefore adversely affected by foreign body reaction, excessive inflammation, and necrosis in the underlying tissues. In studying bronchial healing, therefore, it is appropriate to study the epithelium as an index of the total healing process. Layers of the bronchial wall deep to the cartilage layer are difficult to study, so in this study the area of interpretation was limited to the epithelium and subepithelial stroma.

Layer-to-layer approximation of tissues was found to facilitate rapid healing as demonstrated in the epithelial and subepithelial layers of group III closures. Layer approximation in the group III type closures (Fig. 3) was made relatively easy by short amputation of the bronchi at the trachea. Pouches, sinuses, and cysts were eliminated as residual areas for accumulation of secretions. In these layer closures there was also a marked reduction in foreign body reaction and pressure necrosis demonstrating the importance of keeping the amount of suture material to a minimum. Despite a thinner zone of approximation, with better anatomic repair the outer fibrous cap in layer closures should heal faster and stronger. Reinforcing the wounds with extrabronchial tissue should help eliminate the disadvantage of having a thinner zone of fibrous healing. From the results in healing (Table II) obvious benefits were seen when silk sutures were placed

FIG. 9. An area with prominent inflammation and necrosis after cauterization of the mucosa in a group II closure.

FIG. 10. Good healing of a group III closure with thick columnar epithelium and a stroma with a minimum of inflammatory and necrotic products.

extraluminally. In group III layer closures in which catgut sutures were used to encompass a greater amount of tissue, pressure on the extramucosal silk sutures was minimized. The silk sutures remained outside the mucosa where they completed the airtight seal and added strength. Absorbable catgut suture material was used for the larger tension-relieving sutures because nonabsorbable sutures which extended into the lumen acted as wicks or niduses for stitch abscesses (Fig. 6). When located in the lumen or in the subepithelial tissue, silk sutures sometimes formed excessive intraluminal granulations which, if left longer, might have progressed to granulomas with strictures. It has been shown that under these circumstances chronic reaction usually occurs until the suture material and all adjacent tissue ulcerates and sloughs into the lumen (Fig. 4) leaving a path of granulation tissue. These sutures may cause distressful coughing until expectorated or removed. Bjork (2) and others are now using catgut for bronchial suturing but many surgeons are reluctant to sacrifice the tensile strength of nonabsorbable materials. Chemical cauterization of bronchial mucosa in this study was of no benefit and often was harmful to bronchial healing.

Certain principles in technique of bronchial wound closure are commonly stressed and are well accepted. These include avoidance of trauma, contamination, excessive suture material, and air leaks. Many surgeons have advocated short amputation of bronchi, reinforcement of bronchial wounds with extrabronchial tissue, and adequate antibiotic therapy.

A principle which has not been given enough consideration in pulmonary resections is that of layer-to-layer approximation. This type of closure, as demonstrated in this study, brings tissue layers together for per primam healing and mucosal sealing of the wound. In contrast to closures with epithelial surface approximation, layer closures allow shorter amputations and extramuco-

sal suturing with minimum strangulation of tissues.

SUMMARY

1. Bronchial wound closures were studied grossly and microscopically after pneumonectomies on 40 dogs.

2. In contrast to closures with epithelial surface approximation, layer-to-layer closures initiated earlier regeneration of thick differentiated columnar epithelium and rapid healing in the subepithelial layer.

3. When nonabsorbable silk sutures extended through the mucosa into the lumen, as in epithelial surface closures, chronic reaction and ulceration resulted. This result was eliminated in the layer-to-layer closures by extramucosal suturing. This layer approximation also eliminated residual bronchial stumps with blind pouches by allowing shorter amputation of bronchi.

4. In one method of layer closure, with amputation of the bronchi at the tracheobronchial junction, absorbable catgut sutures were successfully used to minimize stress on the extramucosal nonabsorbable sutures.

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THE REGIONAL HEMODYNAMICS OF CHRONIC EXPERIMENTAL ARTERIOVENOUS FISTULAS

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INFORMATION is available on changes in heart rate, heart size, venous pressure, right atrial pressure, blood volume, and arterial pulse pressure in chronic arteriovenous fistulas from several excellent studies. However, no data are available on either the total volume flow changes through such a communication with passage of time or the alterations in distribution of flow through the various limbs of the fistulous communication.

No generally accepted explanation has been offered for the clinical observation that in one patient with an arteriovenous fistula cardiac failure will develop in relatively few months while another patient with a clinically comparable fistula will go along for many years showing no evident ill effect from the abnormal communication.

Newer electronic techniques have made it possible to study both pressure and volume flow in the intact vessels comprising the various limbs of experimental chronic arteriovenous fistulas. The results of such a study are herein reported.

METHODS

Side-to-side arteriovenous fistulas were created in one group of dogs between the femoral artery and vein and in a second group between the common carotid artery and the external jugular vein. These sites were chosen since they were known not to produce immediate cardiac failure and one group of fistulas was cephalad to the heart while the other was caudad. An oval window was excised from the venous wall 10 to 15 millimeters in length and 2 millimeters in width at its center. The margins of the incised arterial wall were sutured to this venous defect with an everting mattress suture. The femoral arteries were 4 to 5 millimeters in diameter and the veins 5 to 7 millimeters in diameter when the fistula was constructed. The carotid arteries were 5 to 6 millimeters in diameter and the jugular veins 5 to 8 millimeters in diameter when the fistula was constructed.

Flow studies were carried out on the individual limbs of the fistula immediately after its construction then repeated at intervals up to 69 weeks. Flow measurements on the various limbs of the fistulas were not performed simultaneously but in sequence as required by the technique of the method employed. Hence, minor variations in flow through one limb might occur while flow through another limb was being measured. The usual close correlation of total inflow with total outflow suggests that such variations were small. Total fistula flow was determined by summation of all inflow or all outflow. These measurements were made by use of the square-wave electromagnetic flowmeter described by Denison and Spencer which permits measurement of both instantaneous and mean flow through exposed but unopened blood vessels. In our hands this instrument could be calibrated to give a flow error of ± 5 per cent.

Pressure studies were carried out in some of the experiments which were undertaken by using the Sanborn capacitance bridge electromanometer.

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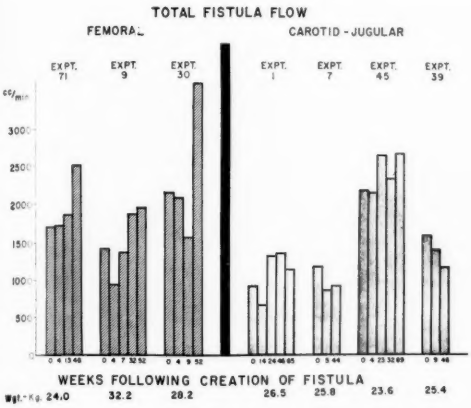

FIG. 1.

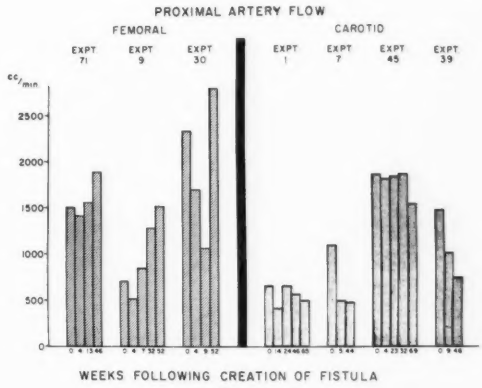

FIG. 2.

FIG. 1. Alteration in total fistula flow through experimental fistulas with passage of time.
FIG. 2. Alteration in flow through proximal artery of experimental fistulas with passage of time.

Four animals with carotid-jugular fistulas and 3 animals with femoral fistulas were so studied.

RESULTS

The alteration in total volume flow through the fistula with passage of time is shown in Figure 1. Flow through the femoral fistulas all increased (47, 40, and 68 per cent) during the course of the interval of approximately 1 year. In 2 of the 3 experiments an initial reduction in flow was exhibited before the later increase appeared. Flow through the carotid-jugular fistulas decreased initially in each experiment while later increasing in 2 of the 4 to a relatively small degree (22 and 24 per cent). In the remaining 2 preparations less flow (23 and 27 per cent) was noted after an interval approximating 1 year than had passed through the fistula at the time of its construction. In 6 of the 7 studies, an initial decrease in total fistula flow was noted while early in the seventh study the flow remained unchanged.

The proximal artery flow studies are charted in Figure 2. In every instance the flow through the proximal artery of the femoral fistulas increased during the study interval while in every instance decrease occurred in this limb of the carotid-jugular fistulas. In each of the femoral studies there was an initial decrease in flow followed by a later increase.

The results of the distal artery flow studies were uniform and are shown in Figure 3. In every experiment dramatic increase in flow through this limb of the fistula was demonstrated. The flow increment appeared to be progressive with passage of time in most of the experiments and had not reached a stable value.

The results of the flow studies in the proximal vein are shown in Figure 4. In 5 of the 7 experiments a rather steady de-

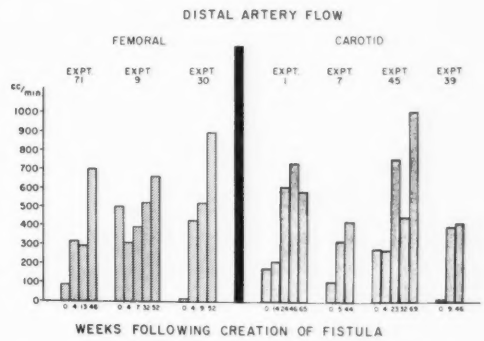

FIG. 3. Alteration in flow through distal artery of experimental fistulas with passage of time.

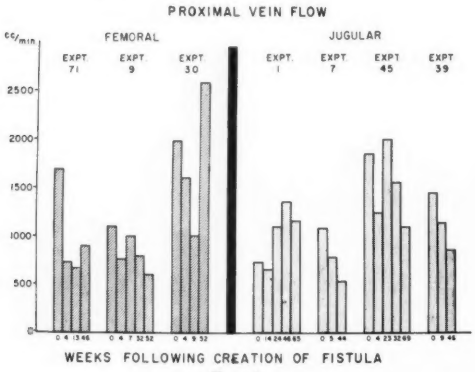

FIG. 4.

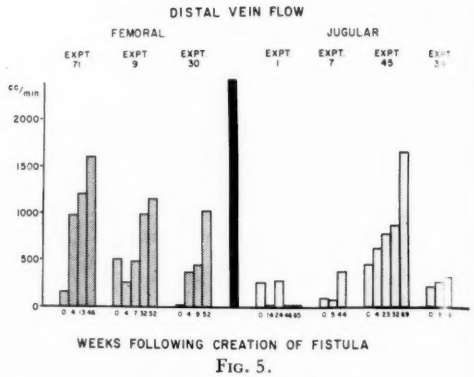

FIG. 5.

FIG. 4. Alteration in flow through proximal vein of experimental fistulas with passage of time.
FIG. 5. Alteration in flow through distal vein of experimental fistulas with passage of time.

crease in flow was noted with passage of time, while in 1 at each site there was an increase.

In all but 1 of the experiments there was a marked rise in distal vein flow with passage of time, as seen in Figure 5. This appeared to be a progressive rise and had not reached a stable value.

The alterations in flow distribution reported in the foregoing are shown schematically for two typical experiments in Figures 6 and 7.

Pressure changes. The alterations in pressure in the various limbs of the fistula which occurred with the passage of time are shown for 2 experiments in Table I. There was little change in proximal artery pressure during the study interval, and pulse pressure did not widen at either site. Distal artery pressure rose appreciably at both fistula locations with passage of time, and it was found that distal artery pressure was maintained even on occlusion of the proximal artery. Proximal vein pressure fell at both sites with passage of time. Proximal femoral vein pressure was found to be negative more often than jugular vein pressure both in acute and chronic experiments. Pressure in the distal vein was always higher in the femoral system than in the jugular system in both acute and chronic experiments. Mean pressure fell with passage of time at both fistula sites with diminution in pulse pressure in the distal vein.

TABLE I.—PRESSURE ALTERATIONS IN VARIOUS LIMBS OF EXPERIMENTAL ARTERIOVENOUS FISTULAS WITH PASSAGE OF TIME

	Femoral fistula Experiment 9		*Carotid-jugular fistula* Experiment 45	
	Immediate	*32 weeks*	*Immediate*	*69 weeks*
Proximal artery....	180/85 (125)	190/115 (145)	195/105 (115)	130/90 (105)
Distal artery.....	55/30 (40)	140/85 (100)	80/55 (65)	90/75 (80)
Proximal vein.....	−2	−10	10	0
Distal vein.....	105/75 (85)	35/20 (30)	60/45 (50)	10

Pressures in mm. Hg.
Mean values in parentheses.

Vessel size. The alterations in diameter of the various limbs of the experimental fistulas are shown for 2 experiments in Table II. The diameter of the proximal artery was strikingly increased in the femoral fistula but was unchanged in the carotid-jugular fistula. This observation would be in accord with the flow changes noted in this particular limb. The diameter of the distal artery was little altered in either location in spite of the rather enormous flow increment through this vessel. All venous limbs invariably had a marked increase in diameter, but this finding was no guide as to alteration in direction of flow with passage of time since flow through some venous limbs increased and through others decreased in spite of marked increment in diameter.

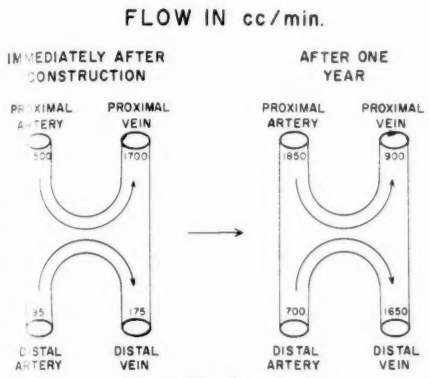

FIG. 6.

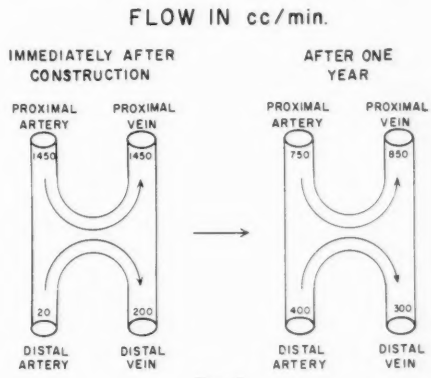

FIG. 7.

FIG. 6. Alteration in flow through experimental femoral arteriovenous fistula after interval of approximately 1 year (experiment 71).

FIG. 7. Alteration in flow through experimental carotid arteriovenous fistula after interval of approximately 1 year (experiment 39).

Pulsatile flow patterns. The alterations in instantaneous flow with passage of time are shown for 1 experiment in Figures 8 through 11. The nature of the flow alterations through the individual limbs immediately after opening the fistula as contrasted to the normal flow patterns in these vessels was discussed in a previous article (7). Most of the flow recordings show both a slow and a fast paper speed. In every instance the time base of the fast paper speed is as indicated in Figure 8. In each flow recording, zero flow is indicated as obtained by momentary occlusion of the vessel. The flow calibration of the individual flow probe used is indicated.

The amplitude of the flow pattern in the proximal carotid artery as seen in Figure 8 diminished with chronicity of the fistula, but this change is probably in part due to alteration in heart rate.

There are 2 alterations of significance in the distal artery flow pattern seen in Figure 9. In each instance, mean flow is toward the fistula but by referring to the position of zero flow it can be seen that a large increment in flow has occurred over the study interval. Also worthy of note is the nature of the systolic flow peaks. Immediately after opening of the fistula, flow is toward the fistula during diastole; then each systole produces a marked reduction in this flow as shown by the inverted peaks on the left in Figure 9. With passage of time and development of collaterals, systolic peaks produce increased flow through the distal artery toward the fistula as seen on the right in Figure 9.

There is little change to be noted in either the pulsatile or mean flow component of the proximal jugular vein flow pattern as seen in Figure 10.

Figure 11 reveals that flow through the distal jugular vein has increased markedly with passage of time and become somewhat more pulsatile.

DISCUSSION

This is not a statistical study, yet certain trends appear consistent enough to enable limited conclusions to be drawn.

TABLE II.—ALTERATIONS IN VESSEL DIAMETER WITH PASSAGE OF TIME

	Diameter, mm. Femoral fistula Experiment 9		*Diameter, mm. Carotid-jugular fistula Experiment 45*	
	Immediate	*52 weeks*	*Immediate*	*69 weeks*
Proximal artery	5	8	5	5
Distal artery	5	6	5	5
Proximal vein	5	8	5	9
Distal vein	5	9	5	9

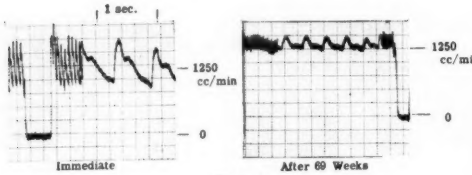

FIG. 8.

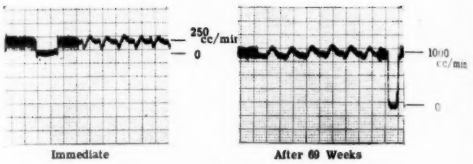

FIG. 9.

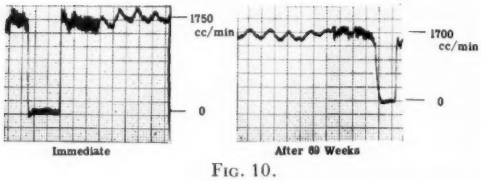

FIG. 10.

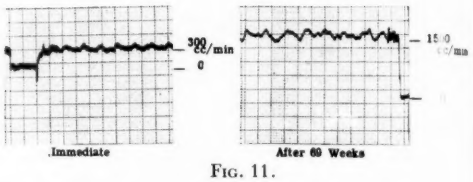

FIG. 11.

FIG. 8. Instantaneous recording of flow pattern in proximal carotid artery of experimental fistula immediately after construction and 69 weeks later.

FIG. 9. Instantaneous recording of flow pattern in distal carotid artery of experimental fistula immediately after construction and 69 weeks later.

FIG. 10. Instantaneous recording of flow pattern in proximal jugular vein of experimental fistula immediately after construction and 69 weeks later.

FIG. 11. Instantaneous recording of flow pattern in distal jugular vein of experimental fistula immediately after construction and 69 weeks later.

The early alteration in total fistula flow, which occurred in the first few months following creation of the fistula, was a distinct surprise. In 6 of the 7 experiments, total fistula flow was reduced at this time from what it had been initially. An entirely erroneous conclusion regarding total fistula flow would have been reached if this time interval had been assumed to be adequate for such fistulas to be labeled "chronic." Moreover, in 2 of the carotid-jugular experiments, the flow was less after an interval approaching 1 year than it had been initially. This is at variance with the classically accepted view expressed by Holman (5) that, ". . . there will be a constant and permanent tendency for the flowing blood to seek the line of less resistance and to be deflected into the fistulous circuit. The inevitable effect, therefore, during the presence of the fistula, no matter how long endured, would be a progressive increase in the volume of blood diverted into the shorter circuit, with a gradual and progressive dilatation of that part of the circulatory system through which the short-circuited blood passes, namely the heart, the proximal artery, the fistula itself, and the proximal vein." Holman immediately pointed out, however, the factors which modify this classical train of events.

Our observations on flow alterations through the proximal artery are also at variance with the statement quoted. While the flow through this limb uniformly increased at the femoral level, it uniformly decreased at the carotid level. This observation regarding a difference in behavior of the proximal artery depending on whether the fistula is cephalad or caudad to the heart supports the clinical observation of Shumacker and Stahl regarding increased hazard of cardiac failure from fistulas caudad to the heart as compared with those cephalad to it. It might also suggest that a postural factor need not be postulated as described by Freeman and Shumacker.

Five of the 7 experiments showed a rather steady decrease in proximal vein flow with passage of time, again a finding at variance with previously expressed views.

In both distal limbs of the experimental fistulas there was a marked increase in flow with passage of time. It would appear that

the flow alterations through the distal limbs had as much, and in several instances more, to do with influencing total fistula flow than resulted from changes in the proximal limbs.

In attempting to evaluate the results here reported and correlate them with previous work, we can do no better than quote again from the monumental contributions of Holman. He stated (4), ". . . the variable effects of an arteriovenous fistula observed clinically are due to variable conditions at the site of the fistula as imposed most probably by the deposition of fibrous tissue, which by its contraction in the course of healing obstructs or limits the fistula itself or one or another of the four cardinal points of the fistula."

The fistulas constructed in this study were all of approximately the same size and between vessels of similar diameter. One set of fistulas, the carotid-jugular, was cephalad to the heart and close to it. The other set, the femoral, was caudad to the heart and more remote from it. The increase in flow with passage of time was no greater through the fistulas closer to the heart than through those more remote. This finding is at variance with the commonly expressed viewpoint which is that the closer a fistula of given size is to the heart, the greater the flow through it. Shumacker has questioned the importance of this relationship. The fistulas constructed cephalad to the heart did show less tendency toward rapid increase in fistula flow than those caudad to the heart, confirming observations made many years ago by Osler. The reason for this difference in behavior at the two sites is not apparent from the current studies. Differences in fibrous reaction about the fistulas at the two levels were not apparent to explain this phenomenon.

It must be pointed out that there is no reason to believe that the flow changes here reported are final and stable values. Five of the 7 animals herein reported are still alive and will be restudied over an indefinite interval.

We have been unable to demonstrate any increase in pulse pressure in the proximal artery at the site of an arteriovenous fistula as reported by Lewis. This work has not indicated a uniform increase in proximal vein pressure immediately after construction of the fistula and, when an initially elevated venous pressure was seen, it fell with passage of time as seen in Table I.

It was somewhat surprising to find the lack of correlation between change in vessel size and vessel flow. Marked increase in flow through a given limb occurred without any alteration in vessel diameter and reduction in flow through another limb occurred simultaneously with striking increase in the diameter of that vessel. Uniform increase in flow through the distal artery occurred without the "constant enlargement of the distal artery" observed by Bosher.

SUMMARY AND CONCLUSIONS

1. Side-to-side arteriovenous fistulas were created between the femoral artery and vein in 3 dogs and between the common carotid artery and external jugular vein in 4 dogs.

2. Pressure and flow studies were carried out in all limbs of the fistulas immediately and at intervals in excess of 1 year after creation of the fistula.

3. Total fistula flow increased significantly after about 1 year in all femoral fistulas. There was also an increase in flow in 2 of the carotid-jugular fistulas but a decrease in the other 2.

4. In 6 of the 7 experiments, total fistula flow was reduced during the first few months after construction of the fistula from what it had been initially.

5. Flow through the proximal artery of the femoral fistulas uniformly increased with passage of time while flow through this same limb in the carotid-jugular fistulas uniformly decreased.

6. In 5 of the 7 experiments, a rather steady decrease in the proximal vein flow was indicated with passage of time.

7. There was a marked increase in flow with passage of time through both distal limbs of the experimental fistulas.

8. The flow values had not become stable at the end of approximately 1 year and there was every indication of future continued change.

9. Increased proximal artery pulse pressure was not observed in these studies.

10. Increase in proximal vein pressure was not always observed; when it occurred the elevated pressure fell to normal with passage of time.

11. There was a distinct lack of correlation between alteration in vessel size and vessel flow with passage of time.

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FOLLOW-UP STUDY OF 500 PATIENTS WITH CHRONIC DUODENAL ULCER ADMITTED TO A VETERANS HOSPITAL

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THIS STUDY was undertaken to examine the clinical course of patients with chronic duodenal ulcer with a view to determining the importance of various symptoms and complications insofar as they might show future course and likely need for surgery.

The records of patients with a diagnosis of duodenal ulcer admitted for the first time to Shaughnessy Veterans Hospital between the years 1947 and 1951 were examined. At this hospital, nearly all patients with chronic duodenal ulcer are admitted for evaluation when first seen at the outpatient or admitting departments. The first 500 in whom a definite diagnosis of duodenal ulcer was reached either by unequivocal roentgenologic findings or at operation were included in this study. In all cases in this series, records of later outpatient or inpatient hospital contacts were studied.

The chronicity of the disease is shown by the fact that in 95 per cent of these patients symptoms had been present for over 2 years at the time of admission. Eighty-five per cent had had intermittent symptoms for 5 years, and 40 per cent for 10 years.

COMPLICATIONS

The following complications were recorded: (1) intractable pain, (2) hemorrhage, (3) duodenal obstruction, and (4) perforation. No instance of pain was reported as intractable unless, as the result of consultation between the medical and surgical departments, failure of adequate response to medical treatment had been accepted and surgical treatment recommended. Intractable pain was considered to be a complication in 43 per cent of the patients in this series. Hemorrhage occurred at some time in the clinical history of 31 per cent of the patients. Duodenal obstruction was not diagnosed unless there was definite objective evidence of gastric retention determined by gastric aspiration, regardless of confirmation by barium meal examination. Objective evidence of duodenal obstruction was obtained in 17 per cent of this series. In 15 per cent of these patients, perforation had occurred at some time in the clinical history. In 10 per cent perforation was treated at Shaughnessy Hospital. The subsequent course of the latter group was of particular interest. In no less than 63 per cent of the 500 patients, one or other of these complications developed during their clinical history. Many had more than 1 complication.

It was of some interest to examine the clinical histories of the 37 per cent in whom complications did not occur. Surprisingly few of these patients admitted to being completely symptom-free. In a very significant number of them, the disease could have been considered intractable to medical treatment. Further it should be noted that the ulcers found at operation in this series were serious. These facts suggest that, despite the high incidence of complicated ulcer, the diagnosis of intractability when made has been well justified.

Surgical treatment of complications was needed in 53 per cent of the total series.

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INTRACTABLE PAIN

Intractability, the most common complication of chronic duodenal ulcer, occurred in 214 cases. In 79 per cent of these, however, it was associated with one or more other complications. The importance of intractability as the most frequent complication of chronic duodenal ulcer is apparent when it is noted that it was the indication for 57 per cent of all the definitive surgery. With the exception of a few patients who either refused surgical treatment or for whom it was contraindicated because of general medical disability, this treatment has already been carried out.

Careful examination of the clinical histories of these patients revealed that in some cases the diagnosis of intractability appeared to have been made after a reasonable trial of medical treatment; however, this was by no means the rule. In far too many cases, there was a history of prolonged morbidity and repeated hospitalizations resulting in significant economic loss. The clinical histories often failed to contain evidence of any serious attempt to detect the characteristics of intractability; namely, progressive increase in frequency, severity, and duration of attacks; decreasing relief of pain by food and alkali; rapid recurrence of ulcer symptoms under normal environmental conditions; recent weight loss; and the onset of vomiting with attacks.

On the other hand, there was far too much stress laid on response to medical treatment in the hospital where the influence of the patient's normal environment could be largely eliminated. Time and again relief of pain was followed by a rapid recurrence after discharge from the hospital and return to normal environment, without the presence of intractability being appreciated.

It is apparent from these records that there is a reluctance to diagnose intractability, despite the fact that definitive surgical treatment may be expected to benefit well over 85 per cent of such patients. Intractable duodenal ulcers will only be diagnosed earlier when physicians examine the long term clinical histories for the early indications of this complication more carefully than they have in the past. Also they must be willing to give less significance to response to treatment in the hospital and more significance to early relapse after discharge from the hospital.

HEMORRHAGE

Next to intractability, hemorrhage, occurring as it did in 31 per cent of the patients, was the commonest complication. Of 118 patients treated for active bleeding between the years 1947 and 1951 at Shaughnessy Veterans Hospital, 94 per cent survived: 77 per cent on medical treatment alone and 17 per cent with a combination of medical and surgical treatment.

The subsequent clinical course of patients surviving on medical treatment alone was studied, and it was found that 14 per cent were free of symptoms, 32 per cent had continuing attacks of pain, and in 54 per cent complications developed which required definitive surgical treatment. This latter figure is no higher than the over-all requirement for surgery in this whole series of 500 cases, which observation suggests that hemorrhage does not markedly decrease the likelihood of a successful long term course of medical treatment.

PERFORATION

Perforation, while less common than either intractability or hemorrhage, occurred at some time during the clinical history of 15 per cent of the patients. Of these perforations, 47 occurred between the years 1947 and 1951 and were treated at Shaughnessy Veterans Hospital. The significant finding was that, of these 47 patients, 62 per cent required definitive surgery for intractable pain, pyloric obstruction, or hemorrhage within an average time of 17 months after perforation. In many of these cases, a careful review of the clinical history often revealed the preperforation existence of these complications. That those patients with established duodenal ulcer and a clinical his-

tory of over 1 year's duration are more likely to require definitive surgical treatment in early postperforation phase was evident.

VOMITING

Pain, the commonest symptom of duodenal ulcer, is followed in frequency by vomiting which occurred in 222 patients. A study of the clinical course of these patients following their first admission with vomiting showed that 68 per cent responded to medical treatment on their first admission with vomiting while 32 per cent did not. Of this latter group, all required surgical treatment at the time, approximately one-third for intractable pain and two-thirds for unrelenting duodenal obstruction. While only 32 per cent of patients who vomited required operation at their first admission, a further 36 per cent were subsequently readmitted for vomiting and required definitive surgical treatment at that time. That a total of 68 per cent of all patients who vomited received definitive surgical treatment is an indication of the grave prognostic significance of vomiting. Of great interest is the fact that vomiting was as often an indication of impending intractability as of duodenal obstruction, as illustrated by the fact that, of 80 patients readmitted for vomiting, definitive surgical treatment was indicated by intractable pain in 42 patients and by duodenal obstruction in 38. The interval after the first admission for vomiting was less than a year in 70 per cent of those with intractable pain; by 5 years 100 per cent had been readmitted. In those with duodenal obstruction, 45 per cent were readmitted in less than a year, and 90 per cent by 5 years. The rapidity with which these readmissions for surgical treatment were necessary, particularly for intractability, is apparent. Finally, it should be stressed that all the 32 per cent of those who vomited and escaped operation had continuing ulcer symptoms.

DUODENAL OBSTRUCTION

Duodenal obstruction, as indicated by gastric retention, occurred in 17 per cent of the patients in this series and was the indication for 30 per cent of all definitive surgery. In each case gastric retention was proved by hour of sleep gastric aspiration, and it was of interest that in 26 per cent of such patients barium meal roentgenologic studies failed to show delayed gastric emptying. Delay in the diagnosis of duodenal obstruction following admission to the hospital has been an outstanding feature in these cases. The magnitude of this problem is illustrated by the fact that in only 15 per cent of the patients was the diagnosis made and operation performed during the first 2 weeks after admission to the hospital.

This delay in the detection of gastric retention was due to three factors; (1) In a significant percentage of cases barium meal studies failed to reveal gastric retention and it was not given further consideration. (2) Hour of sleep gastric aspirations were not carried out routinely during the early postadmission period. Not infrequently several weeks were allowed to pass before hour of sleep gastric residue was measured. (3) The fact that partial gastric retention might exist in the absence of vomiting, particularly when a slowly progressing duodenal obstruction was occurring, was not generally appreciated. Such patients adjust to this slowly increasing partial gastric retention and accommodate by a gradually decreasing intake of food. This fact is reflected by weight loss. It is extremely important, therefore, to examine the patient's history very carefully for any recent evidence of weight loss even in the absence of vomiting and, when such has occurred, to suspect partial duodenal obstruction and gastric retention.

Of the 84 patients with organic duodenal obstruction, 58 received definitive surgical treatment upon diagnosis; 21 responded temporarily to medical treatment, but subsequently—in an average time of 29 months after diagnosis—17 were operated upon, 1 refused operation, 1 was medically unfit, and 2 died from other causes; 2 patients have had continuing symptoms; and in 3 there was no follow-up study.

Perusal of the clinical history of those 17 patients who responded temporarily to medical treatment indicated that the majority had recurring partial obstruction very soon after leaving the hospital; some were even sent home with a tube to carry out hour of sleep aspirations on themselves. A continuing satisfactory response to medical treatment once gastric obstruction had been demonstrated almost never occurred. We believe that the demonstration of organic duodenal obstruction as manifest by gastric retention is an absolute indication for the recommendation of definitive surgical treatment. In our opinion, there is always a significant degree of underlying scar stenosis in all patients demonstrating duodenal obstruction. While an element of edema may be temporarily relieved in the hospital by medical treatment, the underlying stenosis is permanent and results in recurring and progressive gastric retention, decreased caloric intake, and weight loss. If these patients are to be benefited before the stage of extreme starvation so frequently reached prior to surgical treatment, gastric retention must be measured in all patients with chronic duodenal ulcer soon after admission to the hospital, and the presence of organic duodenal obstruction should be suspected in all patients exhibiting weight loss, even when significant vomiting has not occurred.

SUMMARY OF RESULTS

Five hundred patients with chronic duodenal ulcer who were first admitted to Shaughnessy Veterans Hospital between 1947 and 1951 were studied.

1. In 63 per cent 1 or more complications developed during the clinical history.

2. Fifty-three per cent have already required definitive surgery; a further 43 per cent have significant continuing symptoms.

3. Intractable pain, the most frequent complication, was the indication for 57 per cent of all definitive surgery and was diagnosed only after unduly prolonged morbidity and economic loss because: (a) The characteristics of intractable pain in the patient's history were not conscientiously looked for. (b) The significance of rapid recurrence of pain in the patient's normal environment after temporary relief in the hospital was not appreciated quickly enough.

4. An episode of bleeding did not increase the likelihood that any particular duodenal ulcer would eventually require definitive surgical treatment.

5. Sixty-two per cent of postperforation patients required definitive surgery within an average time of 17 months for intractable pain or duodenal obstruction. The percentage requiring definitive surgical treatment was much higher in those with a preperforation history of over 1 year's duration.

6. Of 222 patients in whom vomiting occurred 68 per cent have already required definitive surgical treatment, 32 per cent have significant continuing symptoms, none has been cured. In patients whose vomiting was temporarily relieved by conservative means intractable pain or duodenal obstruction frequently developed for which definitive surgical treatment was required within a short period of time.

7. Organic duodenal obstruction, occurring to some degree in 17 per cent of patients and the indication for 30 per cent of all definitive surgery, was diagnosed very late because: (a) In 26 per cent barium meal studies failed to reveal retention. (b) Gastric residue was not measured until long after admission to the hospital. (c) It was not appreciated that weight loss, in the absence of vomiting, is often an early sign of slowly progressing duodenal obstruction and gastric retention.

8. When duodenal obstruction occurred it proved intractable to medical treatment in nearly two-thirds of patients upon diagnosis. In most of the remaining one-third, while responding temporarily, obstruction recurred and definitive surgery was needed in the first 2 years after diagnosis.

REPAIR OF BENIGN STRICTURES OF THE BILE DUCT INVOLVING BOTH OR SINGLE HEPATIC DUCTS

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THE TREATMENT of biliary strictures in which the bifurcation of the hepatic duct has been destroyed or in which only one hepatic duct is involved presents a problem. Our experience with 40 patients with strictures involving this location in the biliary ductal system will be presented in this report. This group of cases is part of a larger series of 501 patients which has been discussed in a previous report (1).

DIAGNOSIS

As is common in all cases of benign biliary stricture, the clinical features of jaundice, chills, fever, abdominal pain, dark urine, light feces, and hepatomegaly are prominent. In patients in whom only one hepatic duct is obstructed, the symptomatology differs from the classical picture in that the jaundice is less intense; pruritus is a prominent feature; the urine is dark but the feces remain normal in color; and only one lobe of the liver is enlarged. This situation has been described by Stafford and Isaacs in patients with unilateral calculous obstruction of the hepatic duct. Since man suffers no ill consequence as the result of hepatic lobectomy, it is somewhat perplexing that obstruction of only one hepatic duct will produce these signs and symptoms.

OPERATIVE PRINCIPLES AND TECHNIQUE

The plan for the surgical treatment of these patients is quite similar to that employed in the usual type of biliary stricture. The evident exception is that the proximal ducts are located and prepared for anastomosis under more difficult conditions. The initial dissection is accomplished as described previously (2), with elevation of the duodenum and head of the pancreas and the location of the distal end of the duct. Once this has been accomplished, the hilus of the liver is searched for identifying landmarks. The pulsation of the common hepatic artery is a useful guide, since the ducts are usually found lateral to this structure. At times a fistula will be present between the proximal ducts and the duodenum. In many cases, opening this fistula and suitable probing will outline the proximal ducts. Occasionally, the obstructed end of the proximal duct will be apparent only as a whitish bulge at the hilus of the liver, in the appropriate location with reference to the hepatic artery. Concentric excavation of the hilus of the liver in the manner illustrated in Figure 1 is carried out if no ducts are visible. Should a ductal structure be encountered during this dissection, the part of the ductal system which has been found can usually be identified by probing. After identification of this structure, appropriate dissection is then carried out in other areas if indicated. Needling the hilus of the liver with an aspirating syringe will often be rewarded by the aspiration of white or golden bile. After suitable preparation of the ends of the ducts has been completed, the decision can be made regarding the type of repair to be used.

If the two hepatic ducts are separated and are reasonably close together, anastomosis of one to the other is performed as shown in Figure 2. The artificial spur so formed is severed and this created common hepatic duct can then be anastomosed to the lower end of the duct, to the jejunum (Fig. 3), or to the duodenum. If the lower end of the duct is suitable for anastomosis, this type of repair is made. These anastomoses can be made over an indwelling Y tube, as previ-

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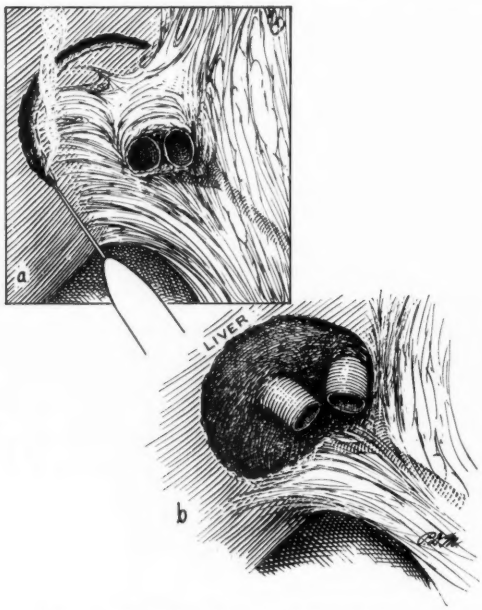

FIG. 1. Dissection of proximal ductal system.

ously reported (3), over a straight tube secured with a single stitch, or over a T tube brought out either above or below the anastomosis.

In some cases, only one hepatic duct can be found in the hilus of the liver. Under these circumstances this duct has been anastomosed either to the lower end of the common bile duct or to a loop of jejunum. The specific operative procedure utilized in making these anastomoses has been outlined previously (2). In those cases in which only the left duct was found, either it was not technically feasible to find the right duct or the right lobe of the liver was atrophied by previous ligation of the right hepatic artery.

When the two separated hepatic ducts have been located by dissection at the hilus of the liver, they are sometimes so far apart that the ends cannot be joined to re-form a common hepatic duct. Under these circumstances, two separate anastomoses must be made. More commonly these anastomoses have been made to the jejunum (Fig. 4b). Usually a prosthesis of straight rubber tubing is secured within each anastomosis by a single silk stitch. If it seems feasible, the lower end of the common duct can occasionally be used in place of the jejunum for either the left or right hepatic anastomosis (Fig. 4a). In this instance, the unused proximal duct is then anastomosed to the jejunum or to the duodenum. An accessory hepatic duct is sometimes found to be involved in the stricturing process. If this duct is of considerable size (about 2 mm. or more in diameter), it must be anastomosed to the jejunum and the main common hepatic duct anastomosed either to the lower duct or to the jejunum.

In some circumstances strictures of only the right hepatic duct have been encountered. In this situation our usual choice of procedure is dilatation of the right hepatic duct with Bakes dilators inserted through the common hepatic duct (Fig. 5). This dilatation should be followed by the insertion of a T tube, with one limb going proximal to the area of the stricture. On 2 occasions a stricture process involving both the right and left hepatic ducts and the common hepatic duct was dilated in the same manner. These procedures are acceptable, of course, only when moderate narrowing is present at the stricture site. If the narrowing is extensive, the ducts should be severed and new anastomoses made.

RESULTS OF SURGICAL REPAIR

It is obvious that any number of combinations of anastomoses may be utilized. Twenty-three different operative procedures were employed in this group of 40 patients (1). The results following these operations in 40 patients with stricture of one or both hepatic ducts are indicated in Table I. The operative mortality of 3 per cent in 60 operations is most satisfactory, considering the difficulties encountered postoperatively in these patients with severe degrees of impairment of hepatic function. This impairment is reflected in the fact that, after leaving the hospital, 10 per cent of the patients died of the complications of liver failure with or

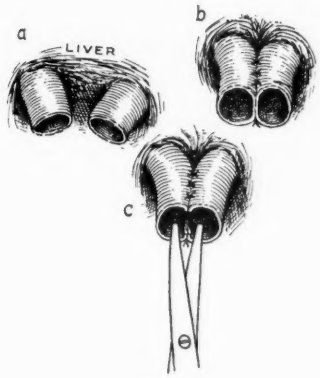

FIG. 2.

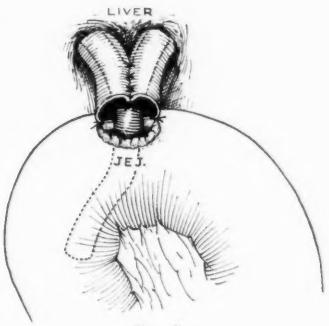

FIG. 3.

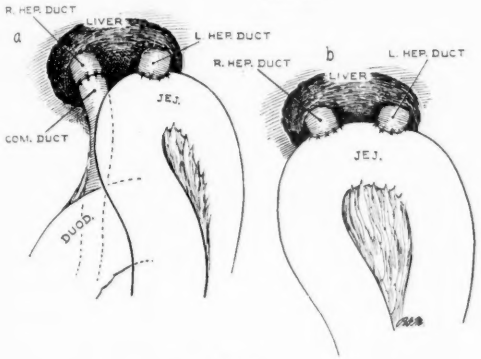

FIG. 4.

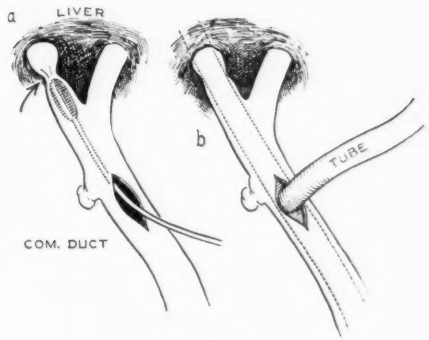

FIG. 5.

FIG. 2. Creation of new common hepatic duct.
FIG. 3. Anastomosis of created common hepatic duct to jejunum over a Y tube.
FIG. 4. a, Anastomosis of right hepatic duct to common duct and left hepatic duct to jejunum. b, Anastomosis separately of hepatic ducts to jejunum.
FIG. 5. a, Dilatation of stricture of right hepatic duct. b, Placement of T tube through dilated segment.

without recurrent obstruction of biliary outflow. Satisfactory results have been obtained in 60 per cent (24 of 40) of these patients (only occasional or no biliary symptoms), in the large majority of cases for 3 years or more after the last operative repair.

The results following the various methods of stricture repair in which the procedure was considered a primary rather than a staged repair are presented in Table II. In 4 patients in whom the bifurcation of the common hepatic duct was completely destroyed, a repair was effected by anastomosis of the right and left ducts, division of the septum so constructed, and anastomosis to the lower duct. In only 1 of these cases was the result satisfactory 3 years or more after operation. Of 5 patients submitted to a similar type of operative procedure with anastomosis to a loop of jejunum, 2 were in satisfactory condition 3 or more years after operation. In 11 instances only the left hepatic duct was located, and this was anastomosed either to the lower end of the duct or to the jejunum. Very few satisfactory results were obtained in this group, as might be anticipated. In 3 patients, the right hepatic duct was found during subsequent explorations. In 11 instances, dilatation of either the right hepatic duct stricture only, or of strictures involving

both hepatic ducts and the common hepatic duct, was carried out. This is obviously not a very satisfactory procedure for such a situation, since the results 3 or more years after operation were satisfactory in only 3 patients.

The results of two stage (Y tube) repairs of these very high strictures are shown in Table III. In this type of repair the anastomosis is constructed over a Y-shaped rubber tube. In the more recent cases, the tubes have contained up to 20 per cent barium. Since it is usually necessary to remove the tube at subsequent operation, these are considered as two stage repairs. The Y tube is very useful in helping to shape the anastomosis during the time that it is in place, and our experience to date with this type of repair in more distal strictures has been most promising (3). For various reasons, only 3 of the patients recorded in Table III had the recommended second stage procedure—removal of the Y tube only. The results in these 3 patients have been satisfactory up to this time. Only a short term follow-up has been possible in 2 of these, however. The results were satisfactory in 3 other patients after only the first stage of the procedure. Of the 17 procedures in which the Y tube was used, only 1 tube has passed spontaneously to our knowledge.

Not shown in these tables are the results after 13 miscellaneous procedures. These include: anastomosis of the right hepatic duct to the lower end of the duct over a vitallium tube; anastomosis of the left hepatic duct to the lower end of the common duct over a Y tube, with one limb of the Y tube inserted into a nonfunctioning right hepatic duct; anastomosis of two proximal hepatic ducts to each other and then to the duodenum over a Y tube; anastomosis of the common hepatic duct and of an accessory hepatic duct to the jejunum over a Y tube; dilatation of a right hepatic duct stricture and insertion of a Y tube; a plastic procedure on a stricture of the right hepatic duct; dilatation of two separate anastomoses of the two hepatic ducts to the jejunum; anastomosis of the common hepatic duct and an accessory hepatic duct to the jejunum; anastomosis of the left hepatic duct to the lower end of the duct and a right hepaticostomy; anastomosis of an accessory hepatic duct to the jejunum and end-to-end anastomosis of the common hepatic duct to the lower end of the common bile duct; anastomosis of the left hepatic duct to the lower end of the common bile duct and the right hepatic duct to the duodenum; and anastomosis of only the right hepatic duct to the jejunum. In another instance, a T tube which had been placed within a high anastomosis and had become occluded was replaced at exploratory operation. The results of these 13 miscellaneous procedures were poor in 7 cases, satisfactory for 3 years or more in 5, and satisfactory for less than 3 years in 1.

DISCUSSION

The situations encountered in this group of 40 patients represent the most difficult ones faced by the surgeon in the repair of benign biliary strictures. Access to the region of these ducts is frequently difficult because of an enlarged liver which interferes with the proper exposure. In other instances, the proximal stumps of the ducts are buried in a mass of scar tissue within the liver substance, and for this reason are difficult to locate and to delineate with sharp dissection. The hazard of entering and damaging the hepatic artery or portal vein is ever present in this dissection. Aside from these impediments, the fact that one is dealing with separated ducts—structures that are half the size of the common hepatic duct—makes the probability of success with anastomotic dilatory or plastic procedures less likely. The fact that satisfactory results have been obtained in 60 per cent of these patients, in the majority for 3 years or more, is a very noteworthy accomplishment. The operative procedures used in dealing with these difficult situations must, of course, be varied and adapted to fit the individual situation. This obviously is the reason for the great multiplicity of procedures that have

TABLE I.—PRESENT STATUS OF 40 PATIENTS* WITH STRICTURE OF THE BIFURCATION OF THE HEPATIC DUCT OR OF SINGLE HEPATIC DUCT

		Dead			Satisfactory result		
Procedure	Total patients	Postop.	Of disease	Poor result	>3 years	<3 years	No follow-up
Anastomosis	28	1	2	6	14	4	1
Dilatation; plastic	9	0	2	2	3	1	1
Anastomosis and dilatation	3	1	0	0	2	0	0
Total	40	2	4	8	19	5	2

*Results after 60 operations on 40 patients; 21 staged procedures; 39 primary repairs.

TABLE II.—RESULTS OF PRIMARY REPAIR OF STRICTURES OF THE BIFURCATION OF THE HEPATIC DUCT OR OF SINGLE HEPATIC DUCTS*

		Dead		Alive		
					Satisfactory result	
Procedure	Total operations	Postop.	Of disease	Poor result	>3 years	<3 years
Ducts anastomosed to each other and to lower end	4	0	0	3	1	0
Each hepatic duct anastomosed separately to jejunum	5	0	0	2	2	1
Left hepatic duct anastomosed to lower end	8	0	0	6	2	0
Left hepatic duct anastomosed to jejunum	3	1	1	0	1	0
Dilatation of right† hepatic duct	9	0	3	2	2	1
Dilatation of both hepatic ducts and common hepatic duct	2	1	0	0	1	0

*Not included are 8 miscellaneous procedures performed only 1 time each.
†Includes 1 case with no follow-up

TABLE III.—RESULTS OF TWO STAGE (Y TUBE) REPAIRS OF STRICTURES OF THE BIFURCATION OF THE HEPATIC DUCT OR OF SINGLE HEPATIC DUCTS*

		First stage			Poor result		Second stage	
		Result			No 2nd stage	2nd stage	Satisfactory result	
Procedure	Total operations	Dead	Poor	Satisfactory			>3 years	<3 years
Ducts anastomosed to each other and to lower end	8	0	7	1	4	3	1	2
Ducts anastomosed to each other and to jejunum	4	1	1	2	1	0	0	0

*Not included are 5 miscellaneous procedures performed only 1 time each.

been employed in treating these patients. When dealing with strictures in which the bifurcation of the common hepatic duct has been destroyed, the procedure of choice is anastomosis of the two ducts one to the other, creation of a new common hepatic duct by division of the septum, and then anastomosis of this created duct to either the lower end of the common bile duct or to the jejunum. Whether or not a Y tube is used depends upon the condition of the proximal ducts; these tubes have been used if the proximal ducts are not suitable for suturing. The choice of whether to use the lower end of the common bile duct or the jejunum depends upon the condition of the lower end of the duct in most instances. Following these procedures, a satisfactory result will be obtained for 3 years or more in approximately 40 to 50 per cent of patients.

In the past strictures involving only the right hepatic duct have usually been dealt with by dilatation and insertion of a T tube, the proximal limb of which passes through the dilated area. That this procedure has not been too satisfactory as a solution to the problem is evident from the results; long-term benefits were obtained in only 3 of the 9 patients. We have been hesitant to sever the right hepatic duct at the location of the

stricture and make an anastomosis, however, because of the inherent technical difficulties involved in this situation.

SUMMARY

Our experience with the diagnosis and the operative treatment of 40 patients with very high strictures of the bile ducts has been described. These strictures involved either the right or left hepatic duct or both, in which case the bifurcation of the common hepatic duct had been destroyed. Sixty operative procedures were employed in the treatment of these 40 patients, and approximately 60 per cent are now well and free from symptoms, the majority for more than 3 years. The procedure of choice for strictures in which the bifurcation of the common hepatic duct has been destroyed is the anastomosis of the right and left hepatic ducts to each other, the creation of a new common hepatic duct by division of the septum so formed, and then anastomosis of this created common hepatic duct either to the lower end of the common bile duct or to the jejunum. This anastomosis may be made over a T tube or a Y tube. Our present treatment for strictures involving only the right hepatic duct is dilatation through an incision made in the common hepatic duct and placement of a T tube, one limb of which goes through the dilated portion of the duct.

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ANESTHETIC MANAGEMENT DURING TOTAL HEPATIC LOBECTOMY

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THE SUCCESSFUL conduct of anesthesia for the operation of total hepatic lobectomy requires a knowledge of the nature, etiology, and therapy of the complications associated with this procedure. It was believed, therefore, that a study of the operative and immediate postoperative course of patients who had been subjected to removal of one of the lobes of the liver would facilitate the future anesthetic management of these cases. The present report includes all cases of total right or left hepatic lobectomy performed at Memorial Center for Cancer and Allied Diseases. Patients subjected to partial hepatic lobectomy or removal of individual metastatic lesions have been eliminated from this study.

SOURCE OF MATERIAL

The material included in this review consists of 36 right and 17 left hepatic lobectomies. Seven of the latter group were performed in association with another operation such as gastrectomy or resection of the colon. There were 19 male and 34 female patients with a variety of malignant and benign lesions of the liver (Table I). Although the majority of individuals were in the fourth, fifth, and sixth decades of life, the age range extended from 16 months (a right hepatic lobectomy) to 73 years (a left lobectomy). The oldest patient subjected to removal of the right lobe was 69 years old.

None of the patients in the present series could be classified as good risks and several were in a severely debilitated condition. In addition to the preoperative complications listed in Table II almost all the patients presented a variety of symptoms relating to the gastrointestinal tract and liver, including moderate to marked abnormalities in various tests of hepatic function. A number were still recovering from the effects of recent surgical intervention.

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CONDUCT OF ANESTHESIA

In the majority of patients removal of the right lobe necessitated a combined thoracoabdominal approach whereas the left lobe could be easily extirpated by the abdominal approach alone. The average duration of time required for anesthesia and operation in right lobectomy was 4 to 5 hours with extremes of 1 hour and 50 minutes and 9 hours and 45 minutes. The total duration of anesthesia was 13 hours in 1 patient under hypothermia. A much shorter time was required for removal of the left lobe of the liver.

The adult patients and older children were induced with thiopental sodium, intubated and maintained in a light plane of anesthesia with the aid of relaxant drugs. Cyclopropane was the major anesthetic agent in 2 patients, and ether in all the others except 1 in whom a combination of thiopental, nitrous oxide-oxygen, and a relaxant was employed throughout the procedure to permit removal of the lobe with

TABLE I.—LESIONS OF LIVER

Diagnoses	*No. of cases*
Benign hepatoma	1
Malignant hepatoma	7
Cyst	2
Hemangioma	3
Hepatocellular cancer	6
Leiomyosarcoma	1
Angiosarcoma	1
Spindle cell sarcoma	1
Cancer of gallbladder with extension to liver	8
Metastases to liver from bowel primary	14
Metastases to liver from primary other than bowel	8
Portal cirrhosis	1
Total	53

TABLE II.—PREOPERATIVE COMPLICATIONS

	No. of cases
Respiratory	
Chronic bronchitis	2
Pulmonary emphysema	2
Dorsal kyphosis	2
Cardiovascular	
Essential hypertension	4
Hypertensive cardiovascular disease	7
Coronary heart disease	3
Rheumatic heart disease	1
Cardiac arrhythmia	4
History of cardiac decompensation	1
History of cerebrovascular accident	1
General	
Pernicious anemia	1
Diabetes mellitus	1
Idiopathic purpura	1
Chronic alcoholism	1

the actual cautery. Hypothermia was used in 1 patient and elective hypotension induced by hexamethonium or arfonad in 2 patients undergoing right hepatic lobectomy.

The infant was induced with open cyclopropane, intubated and maintained on ether by means of the Heidbrink infant circle apparatus.

OPERATIVE COMPLICATIONS

The operative course was completely uneventful in 19 patients of the present series, 9 of whom were subjected to right hepatic lobectomy and 10 to removal of the left lobe. Excessive loss of blood with its associated physiologic changes was the major complication in the remaining 34 cases. Although the volume of blood replacement in right hepatic lobectomy ranged from 2 to 32 pints during the course of operation, almost half of the patients received over 10 pints of blood and 7 patients 20 or more pints. The blood loss in left hepatic lobectomy was comparatively small with a maximum replacement of 7 pints and an average of 2 to 4 pints.

Previous investigation of the complications of massive blood replacement has shown that they can be grouped into two major categories: (1) a hemorrhagic diathesis and (2) disturbances of cardiovascular function. Excessive oozing from the operative site occurred in 9 cases in which right hepatic lobectomy was performed. Seven of these patients received from 5,500 to 15,000 cubic centimeters of blood whereas the remaining 2 were transfused with 2,000 and 3,000 cubic centimeters respectively.

It is unfortunate that the operating room cardioscope was not employed in every case in the series, since, without its use, it is impossible to determine the exact number of cases in which serious cardiovascular arrhythmias and other abnormalities of the electrocardiogram were present during the operative procedure. In 6 documented cases, 5 right and 1 left lobe plus a gastrectomy, a variety of electrocardiographic changes were associated with the rapid administration of large volumes of blood. These included bradycardia, nodal rhythm, prolongation of the QT interval, peaking and elevation of the T wave, bundle branch block, multifocal ventricular premature contractions, ventricular tachycardia, cardiac asystole, and ventricular fibrillation. In 1 patient electrocardiographic changes consistent with tetany responded to the intravenous administration of calcium gluconate.

Traction on the vena cava with associated reduction in venous return to the heart and marked fall in blood pressure occurs during the course of right hepatic lobectomy as a result of displacement of the liver preparatory to division of the hepatic veins. This sequence of events was found in 6 cases of the present series. Entrance of air into the vena cava secondary to a small rent produced a transient episode of imperceptible blood pressure and pulse in 1 patient. The cardiovascular system was restored to normal by the administration of 20 milligrams of vasoxyl.

Another serious complication occurred in a 45 year old male patient subjected to left hepatic lobectomy for advanced cirrhosis of the liver. This patient was chronically ill with marked ascites and myocardial disease. During the course of operation he received 2,000 cubic centimeters of blood, 600 cubic centimeters of plasma, and 1 unit of antihemophilic plasma to replace an estimated blood loss of 1,500 cubic centimeters plus

4,000 cubic centimeters of ascitic fluid. At the end of operation cardiac decompensation with pulmonary edema and elevated venous pressure was noted for the first time. The administration of a digitalizing dose of lanatoside-C associated with other appropriate therapy resulted in a restoration of compensation.

There were 6 deaths in the operating room, 5 during the course of removal of the right lobe and 1 during a left hepatic lobectomy associated with a total gastrectomy. All but 1 of the fatalities was directly attributable to excessive blood loss necessitating massive blood replacement. In the sixth case death resulted from inadvertent division of the blood supply to both the right and left lobes. Although this patient died within 15 minutes after ligation of both pedicles, a second patient with a similar situation survived the operation for 3 days. In the latter case the left hepatic artery, unknown to the surgeon, had thrombosed as a result of previous operative intervention.

POSTOPERATIVE COMPLICATIONS

In the group of 47 patients who survived the operation 3 expired within the first 24 hours after surgery and 12 at a later period during the postoperative course. The time and cause of death of each of these patients are enumerated in Table III.

Thirteen of the remaining 32 patients (9 left and 4 right hepatic lobectomies) had a relatively uneventful postoperative course. The other 19 patients sustained a variety of metabolic, respiratory, and surgical complications. These included disturbances of the clotting mechanism with excessive oozing, electrolyte imbalance, protein deficiency, biliary peritonitis, mild pneumonitis or atelectasis, and 2 patients with hepatic insufficiency who survived after proper therapy.

DISCUSSION

In the present series the major cause of death in the operating room and the immediate postoperative period was excessive loss of blood requiring multiple transfusions.

TABLE III.—DEATHS IN POSTOPERATIVE PERIOD

Patient	*Operation*	*Death, days after operation*	*Cause of death*
1	Right hepatic lobectomy	0	Massive blood loss
2	Right hepatic lobectomy	0	Massive blood loss
3	Left hepatic lobectomy, partial pancreatectomy, splenectomy	0	Massive blood loss
4	Left hepatic lobectomy	2	Cerebrovascular accident
5	Right hepatic lobectomy	3	Infarction of liver
6	Right hepatic lobectomy	4	Combined hepatic and renal failure
7	Left hepatic lobectomy for cirrhosis of liver	5	Cardiac decompensation
8	Right hepatic lobectomy	8	Combined hepatic and renal failure
9	Right hepatic lobectomy	8	Combined hepatic and renal failure
10	Right hepatic lobectomy	12	Fecal peritonitis
11	Right hepatic lobectomy	14	Combined hepatic and renal failure
12	Right hepatic lobectomy	25	Combined hepatic and renal failure
13	Right hepatic lobectomy	27	Fecal peritonitis
14	Right hepatic lobectomy	35	Combined hepatic and renal failure
15	Right hepatic lobectomy	60	Repeated hemorrhages from liver

In addition, in several patients who survived the procedure a hemorrhagic diathesis or cardiovascular complications attributable to massive blood replacement developed.

Howland and his co-workers (2, 3) found, by constant monitoring of patients with the operating room cardioscope, that extremely rapid or excessive administration of blood could produce either ventricular fibrillation or cardiac asystole. These untoward effects occurred in cases of adequate blood replacement and were preceded by premonitory signs of bradycardia, prolongation of the QT interval, distortion of the QRS complex, and elevation of the T wave. The exact etiology of the cardiovascular changes asso-

ciated with massive blood replacement is still a matter of conjecture, but several factors capable of producing cardiac irritability are present in cases of multiple transfusions of bank blood. These include elevation of the potassium level, decrease in *p*H, hypothermia, and a shift in the oxygen dissociation curve to the left.

The relatively frequent occurrence of abnormal oozing tendencies in patients transfused with large quantities of blood led Zucker and her co-workers (4, 5) to study clotting factors, platelets, fibrinolysis, and citrate concentration in a series of 12 patients subjected to partial or complete removal of one of the lobes of the liver. These investigators found a greater incidence of fibrinolytic activity during the course of hepatic extirpation than during other radical operative procedures. In addition, 1 patient in the present series showed increased fibrinolysis in the immediate postoperative period. The rapid decrease in platelet count that occurred during surgery is readily attributable to the relative scarcity of platelets in bank blood. Zucker also discovered that after excision of large portions of the liver, prothrombin and factor VII (proconvertin, SPCA, stable factor) fell from normal preoperative values of over 70 per cent to less than 40 per cent within 4 days and remained below normal limits up to 38 days after surgery. Although factor V (accelerator globulin, proaccelerin, labile factor) did not usually reach as low levels as factors VII and prothrombin, it showed a more rapid decline in value and a speedier return to normal levels. These results were not unexpected since the liver is necessary for the production of prothrombin and factors V and VII. There was also a consistent relationship between the change of concentration of the clotting factors and the amount of liver tissue removed.

The hypothermia resulting from the administration of large quantities of cold bank blood may produce a depletion of factors V and VII, prothrombin, and fibrinogen. A prolonged bleeding time, reduced platelet count and increased clotting time have also been demonstrated under conditions of decreased bodily temperature.

The problem of "citric acid intoxication" was studied intensively by Howland and his co-workers (1). These investigators concluded that the average patient possesses a sufficient reserve supply of mobilizable calcium to prevent any marked decrease in plasma ionized calcium during the course of the administration of even large quantities of citrated blood. This may not be true, however, in children, patients under hypothermia or those with impaired circulation or impaired calcium metabolism. Zucker and co-workers found no differentiation between the decay curve of citric acid in hepatectomized patients and those subjected to other operative methods. From these data it is clear that the liver is not essential to the metabolism of citric acid.

Since one or two of the factors mentioned can be present without any evidence of excessive oozing, Howland, Zucker (4, 5), and others concluded that a combination of several factors is necessary for the development of this untoward complication.

The treatment of the cardiovascular complications of massive blood replacement is largely prevention. An operating room cardioscope is almost an essential in the management of patients scheduled for right hepatic lobectomy. Another important factor is the determination of blood loss by volumetric and gravimetric methods with accurate blood replacement as it is lost. Should the electrocardiogram indicate bradycardia, elevation of the T wave, distortion of the QRS complex, or prolongation of the Q-T interval, the administration of blood must be stopped and a plasma expander or saline solution substituted until the picture reverts to normal.

Mild cases of oozing during operation will usually cease as soon as the operation is finished. The most effective therapy for the more severe cases is the administration of lyophilized (antihemophilic) plasma which contains almost normal concentrations of

prothrombin and factor VII and has some degree of antifibrinolytic activity. In addition to the antihemophilic plasma, a few patients in the present series required measures to combat special deficiencies. These included the administration of fibrinogen and fresh whole blood in plastic containers with its content of fibrinogen, platelets, and prothrombin precursors. Although premarin® seemed to produce effective control of oozing in 2 patients, it was difficult to evaluate since other therapeutic measures were also used. Except in the special cases of inadequate depot supplies, calcium is not essential to control excessive oozing due to massive blood replacement.

Since excessive bleeding was a major complication in right hepatic lobectomy, hypothermia was employed in 1 case and controlled hypotension in 2 patients in an effort to reduce the amount of blood loss. No obvious advantage was noted with either technique but the number of cases was too small to justify any significant conclusions.

An attempt was made to correlate the amount of blood loss during surgery with the postoperative course of the patient, especially with respect to the development of hepatic and renal insufficiency. All 6 patients who died during the postoperative period with a diagnosis of combined hepatorenal failure had a history of periods of marked hypotension due to massive blood loss during operation or excessive plasma loss with poor replacement in the first few days after operation. However, hepatorenal failure developed in only 1 of 6 other patients who survived after equally massive bleeding and hypotension. A seventh patient who had received a relatively small quantity of blood also showed evidence of hepatic insufficiency from which she recovered with appropriate therapy. From these findings it is evident that massive blood replacement and prolonged hypotension are not the sole etiologic factors in the development of later hepatic and renal failure.

Unless the anesthesiologist is aware of the cardiovascular effects attendant upon rotation of the liver with subsequent traction on the inferior vena cava, the resultant hypotension may be attributed to other causes leading to inappropriate therapy, such as unnecessary blood replacement. Release of traction by the surgeon effects prompt restoration of cardiovascular function in the majority of cases.

SUMMARY AND CONCLUSIONS

1. The conduct of anesthesia and the operative and postoperative course of 36 patients with right and 17 with left total hepatic lobectomies have been reviewed.

2. The major complications in this series consisted of excessive blood loss with its attendant physiologic complications and the cardiovascular effects of traction on the vena cava.

3. Anesthesia per se played an insignificant role in the development of these complications. The main role of the anesthesiologist is the prompt recognition and therapy of the complications inherent in the nature of the operation.

4. With the exception of marked bleeding in the first 24 hours after operation there was no significant correlation between the severity of the operative complications and the development of untoward sequelae in the postoperative period.

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SERUM AMYLASE LEVELS IN EXPERIMENTAL INTESTINAL OBSTRUCTION WITH SPECIAL REFERENCE TO THE ACUTE AFFERENT LOOP SYNDROME

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HIGH CLOSED LOOP intestinal obstruction involving the proximal (afferent) limb of a Billroth II gastrectomy is a serious problem which sometimes complicates gastric surgery. Acute pancreatitis may be simulated because of the high serum amylase values sometimes present. It is apparent that diagnostic confusion between acute pancreatitis and high intestinal obstruction is extremely serious because of the divergent forms of treatment required in these conditions. A fatal outcome may result if surgical intervention is delayed because of suspected pancreatitis.

Serum amylase elevations may occur in various types of intestinal obstruction. Byrne and Boyd found serum amylase elevations in dogs with experimental mechanical small bowel obstruction, either high or low, if the animals were allowed to eat. They attributed this observation to an increase in intraduodenal pressure induced by obstruction and vomiting, resulting in a rise in pancreatic ductal pressure with mild interstitial pancreatitis. According to Hiatt, serum amylase elevation in experimental strangulated obstruction is related to the amount of actual mucosal necrosis present. Pfeffer, Staisor, and Hinton produced acute hemorrhagic pancreatitis with serum amylase elevations in dogs by creating a very short closed loop duodenal obstruction (from just below the pylorus to just below the main pancreatic duct).

The experiments forming the basis of this report were designed to simulate the conditions of proximal (afferent) loop obstruction following the Billroth II type of gastrectomy with particular reference to changes in the serum amylase level. In addition, certain other animal groups were studied to provide control and comparative data from other areas of the intestinal tract.

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METHODS

Fifty-two normal mongrel dogs were used in this study. Serum amylase determinations were made according to the method of Somogyi. Normal values under the conditions of these experiments were in the range of 700 to 1,000 milligrams per cent, each dog serving as his own control. The determinations were made at 6 to 8 hour intervals for the first 24 hours after operation and then at 12 to 24 hour intervals in those dogs which survived longer. Control determinations were made just prior to operative procedures, and autopsy of each animal was performed as well as microscopic examination of the pancreas.

Group A consisted of 13 dogs with high closed loop (duodenal-jejunal) obstructions to simulate afferent limb obstruction following Billroth II gastrectomy. This condition was produced by ligating the duodenum just distal to the pylorus and the jejunum 15 centimeters distal to the "ligament of Treitz."

Group B consisted of 4 dogs with strangulated jejunal obstruction produced by umbilical tape ligation of the base of a 30 to 40 centimeter jejunal loop in such a manner

as to obstruct both the blood supply and the intestinal lumen.

Group C consisted of 12 dogs with segments of jejunum which were ligated to produce closed obstruction but without strangulation.

Group D consisted of 8 dogs with segments of colon which were ligated to produce nonstrangulating intestinal obstruction.

Group E consisted of 15 dogs with segmental intestinal infarction without obstruction produced at various levels including jejunum, ileum, and colon by mesenteric blood supply ligation.

These experimental groups with results are summarized in Table I.

TABLE I.—SUMMARY OF RESULTS

Group	No. dogs	100 per cent rise		50–100 per cent rise	0–50 per cent rise
		No.	per cent		
A. High closed loop, duodeno-jejunal	13	9	69	0	4
B. Strangulated obstruction, jejunal	4	1	25	0	3
C. Closed loops, jejunal	12	0		1	6
D. Closed loops, colon	8	0		2	6
E. Infarction, various levels	15	2	13	0	2

RESULTS

In group A, high closed loop (duodenal-jejunal) obstructions were produced to simulate afferent loop obstruction in patients with Billroth II gastric resections. Nine or 69 per cent of the 13 animals in this group had a serum amylase rise of more than 100 per cent above the controls. The remaining 4 animals in the group had slight elevations, but they were less than 50 per cent above the controls. At autopsy these animals showed severe distention of the obstructed duodenal-jejunal loop and some had gangrenous bowel changes from the marked intraluminal pressure. Mild to moderate degrees of interstitial pancreatitis were present in these animals.

In group B, with strangulated jejunal obstructions, a serum amylase rise of over 100 per cent above the control value developed in 1 out of 4 dogs (25 per cent). The other 3 animals in this group had slight elevations with less than a 50 per cent increase over the control value. There was no microscopic evidence of pancreatitis.

In group C, with simple closed jejunal loops, there were no instances of amylase values greater than 100 per cent above the control. One animal of the 12 had a rise to between 50 and 100 per cent; there were 6 animals with no or a slight elevation.

In group D, 8 animals with simple closed colon loops, there were no elevations of 100 per cent or more. There were 2 dogs with elevations of between 50 and 100 per cent, and the amylase level was normal in 6 other animals.

In group E, 15 dogs with intestinal infarction without luminal obstruction at various levels, there were 2 animals (13 per cent) in which there was a serum amylase rise of more than 100 per cent above the controls.

The experimental group with the most consistent serum amylase elevation (69 per cent) was group A with the high closed loop duodenal-jejunal ligations designed to simulate the clinical syndrome of acute afferent limb obstruction following Billroth II gastric resection. The only other significant elevations occurred in animals with intestinal necrosis, with or without luminal obstruction. No definite amylase rise was present in the dogs with simple closed loop obstructions not involving the duodenum.

DISCUSSION

There are two postulated mechanisms for serum amylase elevations from intestinal obstruction. The first is duodenal hypertension with back pressure into the pancreatic ductal system resulting in the regurgitation of pancreatic enzymes into the blood; and second, the possible peritoneal absorption of pancreatic enzymes subsequent to contamination from permeable gangrenous bowel or following intestinal perforation. The results of this investigation give support to these concepts. Duodenal hypertension was the most consistent mechanism noted in this study which produced varying de-

grees of pancreatitis with high serum amylase values, with or without the presence of intestinal necrosis. There were no instances of significant serum amylase rise in animals with simple closed loop obstructions unless the closed loop included the abdomen. It is important to note that 13 per cent (group E) of the animals with intestinal necrosis without luminal obstruction did have high serum amylase values. This observation clinically simulates acute mesenteric vascular occlusion.

SUMMARY AND CONCLUSIONS

1. Closed afferent limb obstructions following Billroth II gastrectomy are known sometimes to simulate acute pancreatitis because of the hyperamylasemia which may develop.

2. High closed loop duodenal-jejunal obstructions were produced and significant serum amylase elevations were observed in 69 per cent of these animals. These experimental preparations closely simulated the clinical syndrome of acute afferent loop obstruction following Billroth II gastric resection.

3. Data are presented showing that the serum amylase may rise significantly in some animals with intestinal necrosis but without luminal obstruction.

4. Simple closed loop obstructions did not produce hyperamylasemia unless the loop included the duodenum or unless intestinal necrosis occurred.

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A CINERADIOGRAPHIC STUDY OF POSTRESECTIONAL ALTERATIONS IN OROPHARYNGEAL PHYSIOLOGY

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IN RECENT YEARS there has occurred a renewal of interest in the physiology of the upper aerodigestive tract, with particular emphasis upon the mechanism of deglutition. The availability of new techniques for study accounts for the increased attention afforded this area. Cineradiography with image intensification has made possible detailed visual analysis of the various stages of swallowing. Improved methods of pressure measurement have clarified the gradients concerned. Electromyographic studies have provided in the experimental animal some understanding of the participation of the individual muscles.

Attention has centered chiefly upon the normal human being, but there has also been some study of the experimentally altered animal and the abnormal human being, particularly those with alterations of swallowing based upon neurologic lesions. There have been occasional isolated reports of studies on patients with alterations due to surgical procedures, accidental trauma, congenital defects, and muscular dystrophies.

It is fortunate that there is a resurgence of interest in the physiology of deglutition, because the emergence of reconstructive surgical procedures in this area demands optimal understanding of concepts of function. Naffziger and associates described a muscle transplantation operation done to improve swallowing in a patient who had a lesion involving the last four cranial nerves. Edgerton has utilized rib grafts to provide forward support of the larynx in patients who have lost surgically the anterior support of the hyoid-larynx column. Douglas has utilized anterior glossopexy to improve airway function in infants born with the Pierre-Robin syndrome (micrognathia, glossoptosis and cleft palate). In all such reconstructive measures designed to correct altered physiology of the upper aerodigestive tract, the importance of complete knowledge of the involved physiology is self-evident. It is possible that as the normal and abnormal physiology are further clarified, additional reconstructive measures, both surgical and nonsurgical, will be conceived. An example of such a development is found in Bosma's (8) use of measures of physical medicine in the rehabilitation of the postbulbar polio patient.

The present study is concerned with an investigation of the dynamics of swallowing in a group of patients who have had surgical alteration of certain structures of the upper aerodigestive tract. It was believed that these patients constituted valuable subjects in whom to observe the effects produced by ablation of various components of the normal mechanism. It was believed to be important to learn how these patients carried out the act of deglutition, to analyze their difficulties, and to understand the compensations achieved. The importance of careful study of such human material is heightened by the fact that species variation is considerable in the dynamics of swallowing.

MATERIALS AND METHODS

A total group of 25 patients has been studied who have undergone varying degrees of surgical operation for cancer upon the structures of the upper aerodigestive tract. These patients were from the surgical services of the Grace-New Haven Community

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TABLE I.—SUMMARY OF SURGICAL ALTERATIONS IN STRUCTURE IN THE 11 PATIENTS STUDIED

Patient Case No.	*Bone, amount resected*	*Muscles detached or resected*	*Other soft tissues resected*
J.O'C. 1	Inner cortex of anterior mandible	Right and left digastrics, right and left geniohyoid, right and left genioglossus mylohyoid (ant. portion)	Bilateral suprahyoid neck dissection-ant. floor of mouth, ant. inferior tongue
A.G. 2	Anterior mandible, from right mental foramen to left	Right and left digastric, right and left geniohyoid, right and left genioglossus, anterior mylohyoid	Chin
A.M. 3	Right hemimandible left to mental foramen	Right and left digastric, right geniohyoid (resected), left geniohyoid (detached), right and left genioglossus, right half of mylohyoid and anterior portion of left half	Right radical neck dissection; anterior floor of mouth
G.M. 4	Right hemimandible	Right digastric, right geniohyoid, right genioglossus, right mylohyoid (part)	Right posterior floor of mouth
P.S. 5	Right hemimandible	Right digastric, right geniohyoid, right genioglossus, right hyoglossus (ant. part), right mylohyoid	Right radical neck dissection, floor of mouth, right superior laryngeal nerve
N.S. 6	Entire mandible, entire hyoid	Right and left digastric, right and left geniohyoid, right and left genioglossus, entire mylohyoid, infrahyoid muscles attaching to hyoid bone	Bilateral radical neck dissection, lower lip, chin, ant. floor of mouth
F.S. 7	Posterior ⅔ of left hemimandible, left half of hyoid	Middle constrictor, left digastric, left geniohyoid, left genioglossus, left mylohyoid (post. part), infrahyoid muscles attaching to left half of hyoid, left faucial and soft palatal musculature	Left radical neck dissection; left soft palate, uvula, and lateral pharyngeal wall. Left superior laryngeal nerve
M.H. 8	Left half of hyoid	Hyoid musculature detached parts of left genioglossus and hyoglossus resected	Left radical neck dissection; left posterior tongue tumor
S.J. 9	Right half of hyoid	Detachment of muscles based upon right half of hyoid	Right radical neck dissection with radon seed implantation into right posterior tongue tumor via lateral pharyngotomy
B.P. 10	None	Right digastric, right stylohyoid	Right radical neck dissection, pharyngeal branches vagus
J.S. 11	None	None	Radon seeds in hypopharynx

Hospital and the West Haven Veterans Administration Hospital. In certain of these the operations were directed toward the pharyngolaryngeal area, and the films of this group are still under study. The patients reported herein are those whose surgical treatment was concerned primarily with the oral cavity and the oropharynx (mesopharynx). The pertinent details on the patients are included in the case descriptions and in Tables I and II.

For this first survey of the pathophysiology of these patients, reliance was placed upon clinical evaluation and cineradiography. The possibilities of further analysis by pressure studies and electromyography are acknowledged. In a few of the cases in the group, both preoperative and postoperative studies were carried out.

The cineradiographic examinations were done with a Phillips image intensifier and a 35 millimeter Arriflex camera at 24 frames per second. This camera speed was selected for purposes of convenience of film examination, editing, and storage. It was also believed that although rapidly moving structures such as the hyoid and epiglottis could be filmed at 64 frames per second the greater detail achieved was not necessary for this analysis. The 35 millimeter film was subsequently reduced to 16 millimeter for study in an analyzing projector. This apparatus made it possible to scrutinize the film sequences in detail and to make sequential tracings of the individual frames. The patients were filmed in the upright position, after imbibition of a 30 to 45 cubic centimeter mouthful of thick barium suspension. They were asked to hold this while filming was begun, and then the camera was centered

TABLE II.—RELATIONSHIP BETWEEN SURGICAL PROCEDURE AND CINERADIOGRAPHIC FINDINGS

Patient Case no.	*Structures defunctionalized*	*Alteration in hyoid motion*	*Alteration in larynx motion*	*Alteration in oral transport*	*Alteration in pharynx transport*	*Laryngeal intrusion*	*Other findings*
J.O'C. 1	Ant. inf. sublingual and lingual muscles	1+	0	0	0	0	Independence of posterior tongue function
A.G. 2	Ant. sublingual muscles, ant. mandible	4+	1+	2+	0	0	Expendability of ant. hyoid support
A.M 3	Ant. sublingual muscles hemimandible	4+	3+	3+	2+	0	Effect of oral operation on pharyngeal transport
G.M 4	Right sublingual muscles, hemimandible	1+	1+	3+	2+	0	Effect of oral operation on pharyngeal transport
P.S. 5	Right lingual and sublingual muscles, hemimandible, sup. laryngeal nerve	1+	2+	3+	3+	2+	Compensatory neck movements
N.S. 6	Entire sublingual muscle, mandible, hyoid	Hyoid absent	3+	4+	3+	0	Absence of separate oral phase
F.S. 7	Mid. constrictor and faucial muscles, ½ hyoid and ⅔ of hemimandible, sup. laryngeal nerve	1+	2+	0	3+	2+	Deviation of larynx toward side operated upon
M.H. 8	Hemihyoid and its muscles	1+	0	0	1+	0	Epiglotic asymmetry
S.J. 9	Hemihyoid and its muscles	2+	1+	0	1+	1+	*Vis a tergo* of tongue demonstrated
B.P. 10	Partial denervation of constrictor muscles	0	0	0	4+	0	Unilateral pharyngeal paresis
J.S. 11	None. Radon seed implant only	0	0		0	0	Pharyngeal engulfment

for the first swallow on the oral cavity. During subsequent swallows the apparatus was directed toward the hypopharynx, after which the bolus was followed in its further downward course. Films were taken in both lateral and anteroposterior views.

PRESENT CONCEPTS OF NORMAL BUCCOPHARYNGEAL DEGLUTITION

As a background for consideration of abnormal deglutition, a brief review of the normal act is necessary. The origins of our knowledge on this subject have been reviewed well by Saunders and associates in 1951 and by Ramsey and associates in 1955. These authors cite the writings of such authorities as Harvey, Boerhaave, Magendie, and Haller. Toward the end of the nineteenth century the process was further elucidated by the pressure studies of Kronecker, Falk, and Meltzer, followed by the early fluoroscopic observations of Cannon. Roentgenologic evaluation was pursued further by Barclay and by Mosher in the second decade of the present century. Much of the more recent work which has been done had to await improvements in roentgenologic, particularly cineradiographic, technique. Most of the descriptions available of deglutition pertain primarily to the transport of thick liquids, and this is true of the account which follows. The transport of solids must involve quantitative differences at least. The basis of this review is in the works of Ardran and Kemp (1), Ramsey and associates, Roberts, Bosma (7), and Saunders and associates. Those who have studied extensively the physiology of deglutition point out the wide variations which exist between individuals within the range of normal. There are also differences to be noted in the initial swallow versus subsequent swallows. Ramsey and associates described two essential features in the transport of the bolus through the organs concerned; those which expand the channel to make room for the bolus, and those which

contract the channel on the tail of the bolus to propel it onward.

The process of swallowing is customarily divided, according to Magendie's thoughts, into three stages: oral, pharyngeal, and esophageal.

For the purposes of the present study, it is necessary to consider imbibition as closely related to deglutition, since some abnormal individuals cannot imbibe without swallowing. An attempt is made in the following paragraphs to describe the separate components of the continuous process of deglutition.

Imbibition. In the case of liquids, imbibition may be achieved by either pouring or by sucking. In the former instance the structures concerned are the labial and facial muscles, plus the jaw which opens to permit the act of drinking. In the case of sucking, the facial musculature acts to make a seal around the straw or nipple, and the infraglossal musculature acts to produce a negative pressure within the mouth. While this is occurring, there must be palatoglossal closure, so that the negative pressures being produced are within the oral cavity alone, lest the material imbibed be aspirated.

Deglutition. Oral stage.—The oral stage of deglutition consists first of a preparatory period in which the ingesta are held in the mouth without being lost either externally through the lips or posteriorly through the fauces. The structures concerned with this phase are the orbicularis oris and the palatoglossal sphincter, consisting of the anterior pillars, soft palate, and tongue.

When the voluntary decision to carry out the act of swallowing is made, the conveyance of the mouthful posteriorly from the mouth through the fauces into the oropharynx is carried out either by a transfer of the entire mouthful or by subdividing it into smaller components. Certain swallow-preparatory motions can be visualized by roentgenography during this phase. The conveyance is accompanied by a movement upward and backward of the hyoid bone, after which the tongue is opposed to the hard and then the soft palate, providing a "stripping wave" to propel all or part of the mouthful posteriorly. If the mouthful is large and only a part is swallowed at one time, the tongue must act in a very complex manner, to hold part of the mouthful and yet convey the part to be swallowed. While holding some of the mouthful and conveying a bolus, it is probable that the backward and downward thrust of the tongue on the part conveyed is less than under the conditions in which the entire bolus is being conveyed. Barclay cited evidence to suggest that a significant negative pressure developed in the pharynx and played a major role in drawing the bolus from the mouth into the pharynx. Subsequent investigations by Rushmer and Hendron have refuted the significance of such a mechanism.

From available evidence it is not possible to determine the relative importance of mylohyoid versus tongue musculature in conveying aliment from the mouth. Experiments by Kronecker and Meltzer showed that denervation of the mylohyoid in dogs produced marked impairment in swallowing, making it necessary for the animal to raise the head to decant the mouthful into the pharynx. In other words, an important component of oral transport had been lost, even though nothing had been done to the tongue. Information on this question in the human has not been available.

The initiation of swallow is under voluntary control, but at some point in its transit the bolus strikes certain receptors in the oropharynx which initiate the reflex arcs controlling the further phases of the act of swallowing, phases which are not under voluntary control. It is possible that the size or other features of the bolus determine the strength of the resultant propulsive effort, i.e., that some feedback of information exists.

Pharyngeal stage.—The conveyance of the bolus through the pharynx normally occurs without escape into the nasopharynx, back into the mouth, or into the larynx. For a portion of its passage the bolus is in con-

tact with the inferior surface of the soft palate as the latter is closing off the possible escape into the nasopharynx. The lateral and posterior pharyngeal walls also participate in this closure. There are two essential components of the muscular action of the pharynx in swallow, according to Negus. One of these is the elevation of the entire pharyngeal tube in an engulfing movement, and the other is the passage of descending peristaltic waves. The engulfment component is probably of importance primarily in the transport of a solid bolus. The peristaltic waves are thought to contribute to the propulsion of liquids and to assist in the clearance of residua from the pharynx. Little has been written about the role of the tongue in this stage, but as seen in lateral cineradiographs, its backward rolling motion appears to contribute significantly not only to conveyance through the faucial arch, but probably to transport in the pharynx as well. This motion has been described by Roberts as providing a *vis a tergo* to the bolus. In addition, the posterior part of the tongue provides a surface against which the peristaltic action of the constrictors can work. Forward motion of the hyoid-larynx column may play a role in opening the pharynx to receive a large bolus.

The mechanisms by which the larynx is protected from invasion by the ingesta are several. Saunders and associates have described a group of separate phases in the second stage of deglutition as follows: "(a) elevation of the larynx, (b) posterior thrust of the base of the tongue, (c) the initial posterior inferior movement of the epiglottis, (d) further elevation of the larynx, (e) final descent of the epiglottis, (f) sphincteric closure of the laryngeal aditus, (g) passage of the peristaltic wave down the pharyngeal constrictor muscles, (h) opening of the superior end of the esophagus, (i) the anterior movement (return) of the base of the tongue to the resting position, (j) return of the epiglottis to the upright position, (k) descent of the larynx to the resting position." Additional mechanism mentioned by Ardran (2) is the tendency for the majority of the bolus to descend via the lateral food channels, thereby largely bypassing the laryngeal aditus. If any barium does enter the laryngeal vestibule, it is later extruded by compression. Thus it is seen that there is a complex of mechanisms protecting the larynx against invasion by ingested material. The mechanisms which have been described are primarily motor, but the sensory components of reflex arcs play a role as well, as evidenced by the fact that superior laryngeal nerve injuries result in problems of inadvertent aspiration.

Esophageal stage.—This is part of another chapter and extends beyond the scope of the present study. At the completion of the act of swallowing, various movements of restitution take place, with re-establishment of the airway. The state of tonic closure of the cricopharyngeal sphincter prevents the entry of air into the esophagus during inspiration.

DESCRIPTION OF PATIENTS STUDIED AND FINDINGS

CASE 1. J. O'C., a 44 year old man, had an epidermoid cancer of the anterior portion of the floor of the mouth which had extended up along the posterior mucosa of the lingual surface of the alveolus. The resection, carried out in December of 1957, consisted of wide removal of the anterior part of the floor of the mouth, including some of the inferior surface of the tongue, plus marginal resection of lingual and dental surfaces of the anterior part of the mandible from right mental foramen to left mental foramen. Muscles sacrificed consisted of anterior ends of both genioglossi, both geniohyoids, both digastrics, and the anterior mylohyoid. A bilateral suprahyoid neck dissection was done in continuity with the resection of the primary tumor. The wounds were closed primarily, but the oral portion of the closure did not heal primarily, healing rather by secondary intent.

Clinical status. This man's over-all disability is slight. The most significant impairment involving speech, in which there is difficulty with the linguodental consonants in particular due to the binding of the anterior portion of tongue to the floor of mouth. He has very little difficulty with swallowing and is able to maintain his weight.

Cineradiographic findings, June 1958. Imbibition is accomplished without difficulty by pouring from a cup. The patient is able to hold the barium in the mouth

until the voluntary initiation of swallowing, indicating competency of glossopalatal (faucial) closure. The picture of the barium-filled oral cavity in the swallow preparatory position is unusual, because of the fact that some of the musculature of the inferior aspect of the anterior portion of the tongue is missing, with the remaining portion bound down to the floor of the mouth at a point midway back along the horizontal ramus of the mandible. This conveys the impression that the tongue volume is reduced by about one-half. Despite the reduction in tongue mass and the binding down of the anterior portion, conveyance of oral contents to the pharynx is accomplished well. A normal "stripping wave" with the tongue broadly contacting the hard palate does not occur. Rather the evacuation of the mouthful is achieved by a combination of decanting plus a repetitive camlike motion similar to that employed by "trick-drinkers."

Transit of the bolus through the pharynx is seen to occur without abnormality. The epiglottis is seen to turn downward during deglutition and to remain down during several swallows, while the hyoid is ascending independently during each swallowing movement. The direction of hyoid motion appears to be altered by the surgical intervention, but it cannot be stated to be beyond the variations of normal. The larynx is seen to ascend normally and no tracheal intrusion of barium occurs. Passage through the cricopharyngeal sphincter occurs in a normal manner as does further transport down the esophagus.

Interpretation. In this patient there has been detachment of the muscle complex arising from the anterior central section of the mandible—genioglossi, geniohyoids, and digastrics, plus alteration of the tongue. Only the anterior, central portion of the mylohyoid is detached. Despite these moderately extensive alterations, compensations occur to permit adequate accomplishment of the oral phase of swallowing. Apparently the retention of functioning elements of mylohyoid is a critical factor in minimizing the impairment. The mechanism of the compensations has been described.

The prompt conveyance through oropharynx and hypopharynx substantiates the assumption that there is considerable independence of function of posterior and anterior portions of the tongue. This theory is in agreement with electromyographic findings of Bosma (10). The lack of any definite effect upon hyoid motion of detachment of geniohyoids and anterior digastrics is of interest. It suggests that these muscles may play little role in the upward-forward movement of this structure, or that compensations for their defunctionalization can occur.

Conclusions. (1) The loss of a large portion of the anterior genioglossus plus detachment of geniohyoids and anterior digastrics results in minimal impairment of the oral phase of swallowing. The relatively intact mylohyoid and the other tongue-hyoid musculature remaining is well able to accomplish oral evacuation, plus conveyance because of the relative independence of posterior tongue function from that of the anterior portion. (2) Surgical detachment of the ventral displacing muscles of the hyoid results in negligible alteration of its swallowing movements.

Case 2. A. G., a white male, was born in 187[illegible]. In 1952, excision of a cancer involving the entire lower lip was carried out, with cheek flap reconstruction, Dieffenbach operation. In 1953, a recurrence developed in the soft tissues of the chin, necessitating a wide excision of all the soft tissues of the chin as well as the mandible from right mental foramen to left mental foramen. Digastric, geniohyoid and genioglossus muscles were detached along with anterior portions of the mylohyoid. A pedicle reconstruction of the soft tissues of the chin was subsequently done.

Clinical status. There is a resultant cosmetic deformity. With the lower half of the orbicularis oris gone, the patient's oral continence is deficient. He uses the tongue as a partial seal of the oral aperture. He is unable to masticate, subsisting on a soft diet, which he swallows well and which maintains a satisfactory nutritional state. He is able to protrude the tongue surprisingly well despite the genioglossus detachment.

Cineradiographic findings, August 1958. Imbibition is carried out by sucking through a straw or by drinking from a cup. Conveyance of the barium from mouth to pharynx is efficiently carried out by miniature "stripping waves" which transport small components of the mouthful. These waves appear to be well organized and integrated.

Transport of the bolus through the pharynx is unimpaired. Upward movement of the hyoid is minimal, and no anterior movement is seen. The larynx ascends a short distance. Despite the subnormal amplitude of movement, no laryngeal intrusion of barium occurs.

Interpretation. In this patient the loss of an anterior segment of the mandibular arch means that there must exist an appreciable defunctionalization of the mylohyoid, since contraction of this muscle serves to draw the two separate mandibular remnants together, thus eliminating part of the upward compression effect upon the oral cavity. Despite this loss, there occurs satisfactory evacuation posteriorward of the oral bolus, which, in this instance, is of thick liquid consistency. It is difficult to guess what muscular forces can compensate for the partial loss of this diaphragmlike mylohyoid action. The transport of smaller boluses appears to be part of the compensation. The turgescent tongue is somehow still able to exert an upward thrust against the hard palate, which, combined with a stripping wave, moves the oral bolus posteriorward. The minimal impairment of tongue protrusion indicates that after the surgical separation of the genioglossus from its mandibular origin, some degree of reattachment can occur, possibly to scar tissue running between the ends of the divided mandible. Similar reattachments may form of the anterior ends of the geniohyoid and the digastric.

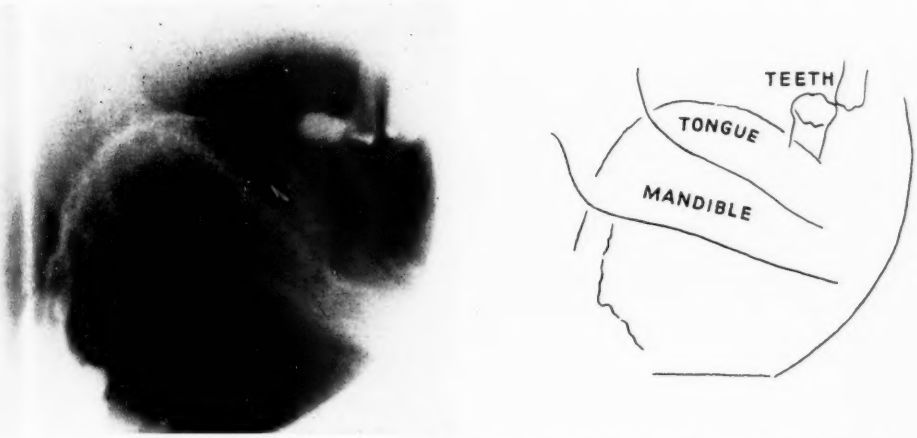

FIG. 1. Case 1. Single frame from cineradiography of a swallow, lateral view of barium-coated mouth, showing fixation of tongue to floor of mouth.

The defunctionalization of the musculature responsible for normal anterior movement of the hyoid during swallowing seems to have little significance, in that satisfactory protection of the larynx from intrusion of ingesta still exists.

Conclusions. (1) Partial loss of the mylohyoid sling mechanism has detectable influence upon the efficiency of the oral phase of swallowing, but compensation for this loss occurs, at least in the swallowing of thick liquids. (2) The anterior component of hyoid travel during swallowing is not necessary for airway protection. (3) Following surgical detachment of certain muscles of the tongue-hyoid complex, even with removal of their bony origin or insertion, reattachments can form which are functionally efficient.

CASE 3. A. M., a white male, was born in 1893. He was seen in 1953 with a large carcinoma of the right inferior alveolar ridge centering at the level of the right mental foramen. The right hemimandible, including the symphysis as far as the left mental foramen, was resected. Most of the adjacent floor of the mouth was resected, and a radical dissection of the right side of the neck was done in continuity. A radical neck dissection on the left side was done several weeks later. The muscles removed consisted of the entire right and the major portion of the left mylohyoid, the right and left digastric muscles, and the right geniohyoid. The left geniohyoid and both genioglossi were detached from bone.

Clinical status. The patient has a so-called "Andy Gump" deformity, with marked loss of the substance of the chin. As a consequence the lower lip is retracted behind the upper. There is difficulty with salivary continence. He can manage a soft diet and is able to maintain his weight. Despite the loss of forward support of the hyoid-larynx column, there has been no problem with maintenance of airway or aspiration.

Cineradiographic findings, December 1957. The patient can imbibe by pouring or by sucking through a straw. Conveyance of barium posteriorly in the mouth is achieved with considerable difficulty, several separate efforts being required. The mouthful is divided into small segments for separate passage to the pharynx. Small stripping waves are seen. The mandibular fragments are seen to rise sharply during the efforts to achieve evacuation of the oral bolus.

Conveyance through the pharynx is slow and inefficient, apparently as a result of poor propulsion by the tongue, which makes repetitive movements. The difficulty involves a loss of the *vis a tergo* function of the tongue during the pharyngeal component of swallowing. As a result, a complete stripping wave is never seen to close on the pharyngeal bolus. Instead of the usual forward ascent of the hyoid and larynx, one sees only sideways rocking of the hyoid, as the larynx is drawn up to it. Despite these abnormal motions, only minimal laryngeal intrusion occurs. The epiglottis is seen briefly and remains erect.

Interpretation. The loss of forward support of the lower lip results in some impairment of oral closure, but satisfactory imbibition can be carried out nevertheless. The complete loss of skeletal and muscular components of the mylohyoid diaphragm results in significant impairment of the mechanisms of oral evacuation, by interfering with the means by which an upward thrust is conveyed through the turgescent tongue against the hard and soft palates. There are other muscles which may be able to produce some upward thrust of the tongue against the palate, namely the styloglossus and the palatoglossus, but these cannot provide the same force for a strong stripping wave as can the sublingual sling of the mylohyoid.

The degree of impairment of pharyngeal transport found in this patient is of interest, since the surgical procedure was limited to the anterior oral cavity. This indicates confirmation in the human of the findings of Meltzer in the dog, namely that a major contribution to the pharyngeal transport of liquids comes from muscles of the mouth and tongue. The defunctionalization of the geniohyoid and mylohyoid has resulted in loss of elevation and forward motion of the hyoid bone. Despite this, satisfactory protection of the airway occurs, demonstrating further the adequacy of the intrinsic muscular sphincters as the protective mechanisms of the larynx.

Conclusions. (1) Complete removal of the mylohyoid sling causes significant impairment of the oral phase of swallowing, for which, however, some degree of compensation occurs. (2) The same surgical procedure limited to the anterior mandibular arch and sublingual musculature can produce definite interference with the pharyngeal phase of swallowing. The exact mechanism of this is discussed. (3) Loss of upward forward support and movement of the hyoid does not necessarily result in problems of airway maintenance or aspiration of ingesta, provided the sphincteric protectors of the larynx are competent.

CASE 4. G. M. is a 65 year old white male. An epidermoid cancer of the right posterior inferior alveolar ridge developed in 1956, for which irradiation therapy was initially administered. This failed to control the lesion, however, so that surgical resection became necessary in October 1957. Operation consisted of resection of the right hemimandible and adjacent posterior floor of mouth, with removal of the major portion of the right mylohyoid muscle, plus detachment of the right geniohyoid, right genioglossus, and right anterior digastric. No mandibular support was utilized. Radical neck dissection was carried out in continuity with the oral resection. None of the tongue itself was removed. The cut edge of the floor of the mouth was sutured to buccal mucosa in the immediate repair.

Clinical status. Postoperative recovery was satisfactory except for problems with infection of the wound in the lower part of the neck. The patient recovered swallowing function to the point of being able to handle a soft diet within a month after operation. It was at the end of this period that cineradiography was carried out. Speech recovery was fair, but difficult to evaluate because of a language barrier.

Cineradiographic findings. There is seen normal positioning of the mouthful of barium in the swallow-preparatory attitude, with competent palatoglossal closure. Conveyance of bolus from the mouth, however, is significantly affected. A well organized stripping wave is not seen, and several very effortful movements of the tongue are made which finally achieve evacuation of the barium after a slow and labored passage.

Although the various muscles contributing to pharyngeal transport appear to be intact, their function is suboptimal, as judged by the slowness of passage and by the large amount of residual barium seen at the completion of swallowing. No barium enters the larynx.

Interpretation. Optimal function of the mechanisms for evacuation of the oral cavity requires an intact supporting framework and an intact muscular sling of mylohyoid. When the hemimandible is resected, the integrity of the oral diaphragm is lost. To some degree the extent of the changes in swallowing function seen in this patient may be related to the fact that only 1 month had elapsed between operation and roentgenographic studies.

The moderate degree of alteration in pharyngeal transport of liquids in this patient is difficult to explain. The surgical procedure has involved primarily the oral cavity, and the effects upon pharyngeal function must be secondary to this. One interpretation is that the kinetics of the tongue have been enough altered to result in an impairment of its contribution to propulsive mechanisms. Despite the surgical alterations the hyoid bone moves adequately and no laryngeal intrusion of barium occurs.

Conclusions. (1) Defunctionalization of the mylohyoid sling can result not only from its removal but also from removal of one-half of its skeletal framework, the hemimandible. (2) The removal of one-half of the mandible and the detachment of its muscles results in alterations in lingual kinetics observable not only in the oral phase but also in the pharyngeal phase of deglutition. A possible explanation for this was mentioned in connection with Case 3.

CASE 5. P. S. was 57 years of age in 1957 when he was seen with an infiltrating cancer of the floor of the mouth on the right side anteriorly. Attempted control by irradiation was not successful, so that surgical resection became necessary in July of 1958. The operation required was a radical dissection of the right side of the neck in continuity with hemiglossectomy, hemimandibulectomy, and resection of the floor of the mouth on the right side. Structures sacrificed comprised the right genioglossus, geniohyoid, and digastric muscles, plus part of the right hyoglossus. With the right hemimandible one-half the mylohyoid was resected. The right superior laryngeal nerve was sacrificed. Direct primary closure was accomplished and uneventful healing took place. Despite a temporary tracheotomy the patient had severe difficulty with aspirational pneumonitis, from which he finally made a good recovery.

Clinical status. This patient has experienced more than the usual degree of difficulty in progressing beyond a liquid diet to soft foods. Persistent coughing on attempted deglutition is his chief problem. Function of the remaining (left) hemimandible is good, and his speech problems are slight.

Cineradiographic findings. The mouth parts are able to assume a swallow-preparatory position with com-

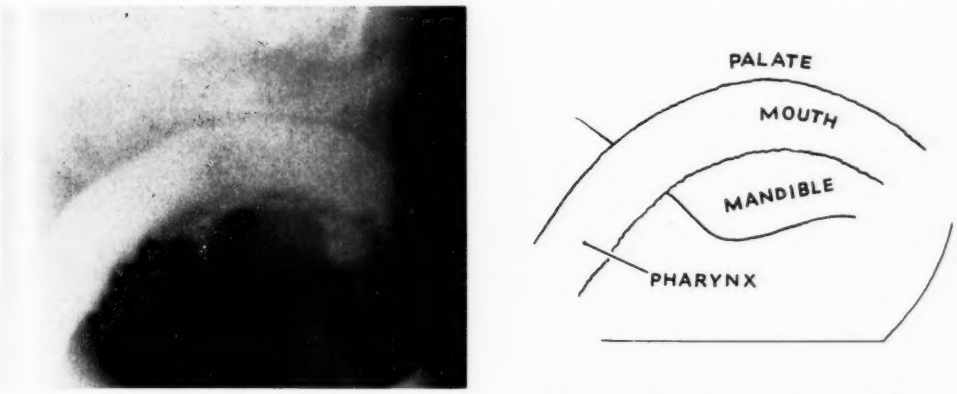

FIG. 2. Case 3. Lateral view of mouth during swallowing of barium, showing unusual shape of barium column.

petent palato-glossal (faucial) closure. Conveyance of bolus from mouth to pharynx is accomplished with dispatch partly by use of compensatory motions, i.e., by tipping the head back and utilizing gravity.

Transport of bolus through the pharynx is markedly impaired, with poorly co-ordinated, dyskinetic movements. The cervical spine extends in attempted compensation for the deficient mechanisms of pharyngeal clearance. An absence of the rollback motion of the posterior part of the tongue usually seen in a normal swallow is noted. Very early in a swallow there is a spillover of barium into the larynx, with the bolus entering the posterior part of the glottic chink. A turning down of the epiglottis is not visualized. Slight nasopharyngeal intrusion of barium occurs during the dyskinetic movements. Hyoid motion appears to be of normal range, but ascent of the larynx is limited. No abnormalities are noted in the penetration of cricopharyngeal sphincter or in transport down the esophagus.

Interpretation. This patient's compensation for the loss of half the tongue plus the mylohyoid expressor mechanism consists of the use of head-tilting to call into play the force of gravity, which achieves satisfactory evacuation of liquids, but, by history, does not permit him to take solids.

Whereas the surgical intervention has involved primarily oral structures, the disability of transport is chiefly pharyngeal. From the roentgenographic views it appears that the deficit in transport is based upon a failure in the rollback motion of the tongue resulting in a diminution of the *vis a tergo* necessary for proper pharyngeal transport of bolus. Whether the loss of this important component is from postoperative scarring or from sacrifice of muscle components cannot be stated. The failure of the mechanisms which normally protect the larynx is assumed to be attributable to sacrifice of the superior laryngeal nerve. The slight nasopharyngeal intrusion is assumed to be related to surgical alteration of the palatal-faucial musculature.

Conclusions. (1) When there is extensive loss of lingual and sublingual musculature, plus loss of supporting skeletal framework, one of the compensating mechanisms which develops for oral conveyance is the use of head-tilting maneuvers in an effort to utilize gravitational force. (2) Surgical operation limited to the oral cavity may, if of sufficient magnitude, defunctionalize the posterior portion of the tongue to a degree which can cause significant interference with the pharyngeal phase of swallowing. (3) Cinefluorography demonstrates the manner in which unilateral superior laryngeal nerve interruption results in laryngotracheal intrusion of ingesta, even though the motor components of the airway protection are intact.

CASE 6. N. S., a white male physician, was born in 1897. He presented at another hospital in 1951 with a large epidermoid cancer involving the inferior alveolus anteriorly with wide local spread. Irradiation therapy had failed to control the tumor. The resection necessary to encompass the lesion included most of the mandible, except for short portions of vertical rami which were initially preserved. Subsequently, the remnant on the right was completely removed. The entire anterior portion of the floor of the mouth was included in the resection, both hypoglossal nerves and the hyoid bone being part of the specimen. The muscles removed thus included the entire mylohyoid, both geniohyoids, both digastrics (anterior bellies), and a large portion of the genioglossus. A radical neck dissection was done on both sides at the time of the resection of the primary tumor. Immediate reconstruction was begun by utilizing a previously prepared bipedicled flap from the anterior portion of the chest. In the reconstruction the remaining segment of tongue became functionally a replacement for the resected floor of mouth.

Clinical status. Numerous reconstructive surgical stages have been carried out, and the patient has

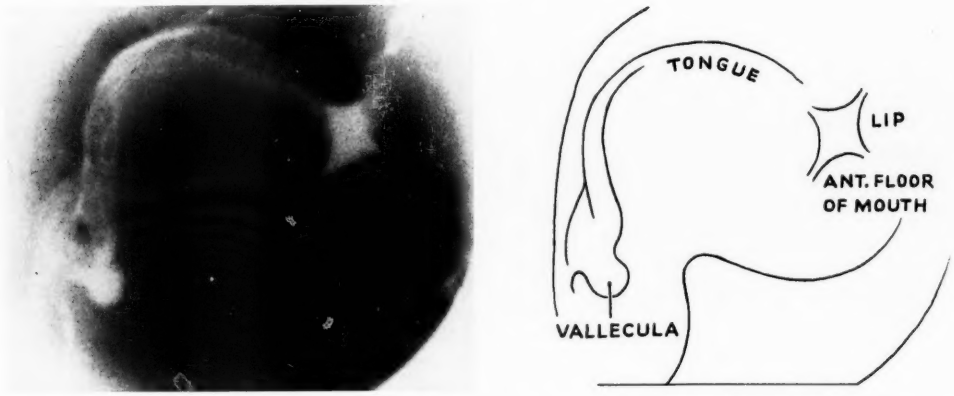

FIG. 3. Case 6. Lateral view of barium-coated mouth at rest. Note absence of mandible and hyoid.

achieved an impressive degree of rehabilitation. He maintains his weight on a blenderized diet of thick liquid consistency which he pours into the mouth from a cup. He cannot suck from a straw. Oral continence is deficient. Speech is moderately impaired, but surprising compensations have occurred for the articulatory elements lost.

Cineradiographic findings. Imbibition is carried out by pouring and results in a slight leakage from the oral stoma. There is no separation between oral and pharyngeal phases of swallow because as soon as the barium is imbibed it proceeds immediately on its descent. The patient cannot prevent the mouthful from proceeding immediately through the faucial arch because of the incompetence of palatoglossal closure. During the transit of the material through the mouth, the small tongue remnant is seen to make cam-like movements as if in an attempt to propel the bolus posteriorly, but these movements are of such small magnitude as to contribute nothing to propulsion of the barium. The anteroposterior view of swallowing shows the unusual shape of the bolus in its transit due to structural alterations.

As mentioned before, there are not truly separate oral and pharyngeal phases in this patient since the mouth functions passively as a funnel through which the aliment is poured on its way to the pharynx. Roentgenograms show a voluminous pharynx which fills rapidly and which empties in an unusual manner. The anterioposterior view shows a repetitive series of small descending pharyngeal constrictor waves, each of which transports a small increment of barium down to the mouth of the esophagus. Very little elevation of the larynx is seen during swallowing, but despite this fact barium does not enter the airway.

Interpretation. In this patient there has been gross alteration of the structures concerned with imbibition and with the oral phase of swallowing. The oral stoma has lost its sphincteric continence and the propulsive mechanism of the tongue-mylohyoid complex has been defunctionalized. The crippled tongue remnant is unable to make a palatoglossal seal so that liquid cannot be held in the mouth to await the voluntary signal for swallowing. The oral stoma and the buccal cavity constitute an inactive funnel through which the ingesta are poured into the pharynx where the act of deglutition actually begins.

With the hyoid bone and mandible removed, there is little musculature remaining which can lift the larynx. Despite the small amount of laryngeal ascent, no laryngeal intrusion occurs. The removal of most of the mandible has probably altered the pterygomandibular raphe origins of the superior constrictor muscle. This fact and the gross alterations of tongue musculature have markedly decreased the mechanisms available for propulsion of bolus through the pharynx. A compensation has occurred in the form of rapid repetition of small propulsive waves.

Conclusions. (1) An intact tongue-mylohyoid complex is necessary for optimal function of the oral phase of swallowing. When surgical intervention defunctionalizes this transport mechanism, the mouth serves as a passive conduit for the passage of ingesta. (2) Palatoglossal closure requires a tongue of sufficient bulk and mobility to be able to make contact with the faucial-palatal structures. Incompetence of such mechanism means that imbibed material will promptly reach the pharynx and initiate the swallow synergy. (3) Elevation of the hyoid larynx column, although a component of normal swallow, is not indispensable. Effective deglutition can occur without tracheal aspiration despite surgical absence of the hyoid and of some of the larynx-elevating musculature. (4) In the normal individual there is a propulsive force which is the result of an interaction between the posterior portion of the tongue and the pharyngeal constrictors transporting the bolus through the oropharynx. When surgical intervention defunctionalizes this mechanism,

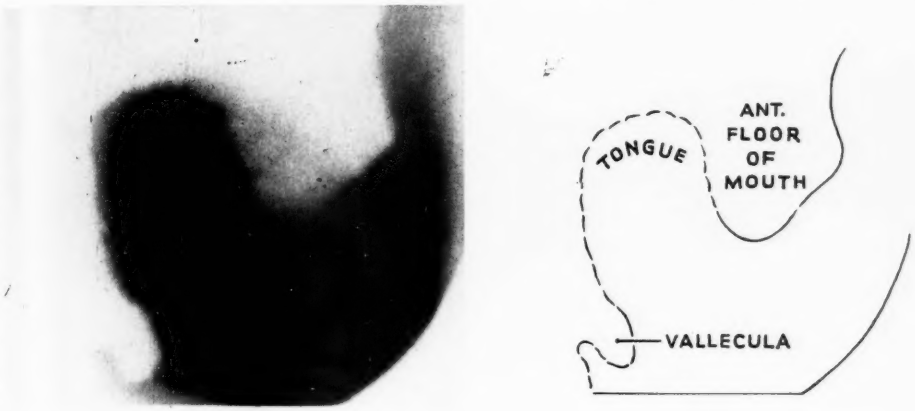

FIG. 4. Case 6. Lateral view during swallowing of barium showing bizarre shape of tongue.

gravitational forces constitute the compensation which occurs.

CASE 7. F. S., a 63 year old white male, had an epidermoid carcinoma arising in the left tonsillar fossa, involving the adjacent soft palate and lateral pharyngeal wall. Attempts to control the lesion by irradiation were not successful so that surgical extirpation became necessary in May of 1956. The operation consisted of a radical dissection of the left side of the neck done in continuity with resection of the primary tumor. Adequate removal of the primary tumor necessitated a wide sacrifice of lateral pharyngeal wall, tonsillar fossa, and soft palate including the uvula. The left half of the hyoid bone with its attached muscles and the posterior two-thirds of the left hemimandible were included in the resection. The superior laryngeal nerve was divided. Only a small portion of the posterior part of the tongue was sacrificed. Primary closure of the defect was accomplished, and uneventful healing ensued.

Clinical status. Postoperatively there was difficulty relearning to swallow, and pulmonary aspiration of ingesta was a problem. Deglutition was impaired to the point that roentgenographic studies, by standard noncinematic technique, were carried out, on one of which examinations the diagnosis was made of a mass in the anterior portion of the neck with complete obstruction of the esophagus and extensive tumor invasion. The subsequent course of events showed that the changes described were actually the result of postoperative alterations. It was necessary to maintain the tracheotomy for a longer period than usual. Eventually, however, the difficulties were surmounted, and the patient became able to maintain his weight on soft foods. His speech is impaired to the extent that he is unable to eliminate nasality because of the insufficient velopalatine closure.

Cineradiographic findings, January 1959. Formation and conveyance of the bolus are accomplished with minimal abnormality. There is escape of barium into the nasopharynx during swallowing.

As of May 1957 and January 1959, the epiglottis is seen briefly. It does not tip downward. In both anteroposterior and lateral views there is seen prompt entry from left posterior of a considerable amount of barium into the larynx and trachea during the act of swallowing. Moderate coughing ensues. Transport through the pharynx is slow and inefficient with considerable retention, particularly in a dilated left pyriform sinus. Only small amounts travel down the esophagus at a time. In the lateral view a bizarre protrusion forward of posterior pharyngeal wall is seen, resembling an exaggerated Passavant's ridge. This presumably represents a contracting mass of superior constrictor muscle which has been detached from its anterior origin. Movements of the remaining half of the hyoid bone are slightly uneven, but are of essentially normal amplitude, both upward and forward. In the anteroposterior view the swallow-ascent of the larynx is seen to be accompanied by marked deviation toward the left, the side operated upon.

Interpretation. The amount of surgical alteration undergone by this patient has resulted in minimal alteration in the oral component of swallowing. The palatopharyngeal insufficiency seen is to be expected from the amount of faucial and palatal tissue resected.

During swallowing there is adequate elevation of the larynx and normal movement of the hyoid remnant. Aspiration of ingesta occurs despite what appears to be adequate function of the motor components of protection of the larynx. This inadvertent aspiration is believed to be the result of a deficit in laryngeal sensation consequent to ablation of the left superior laryngeal nerve. Loss of the sensory com-

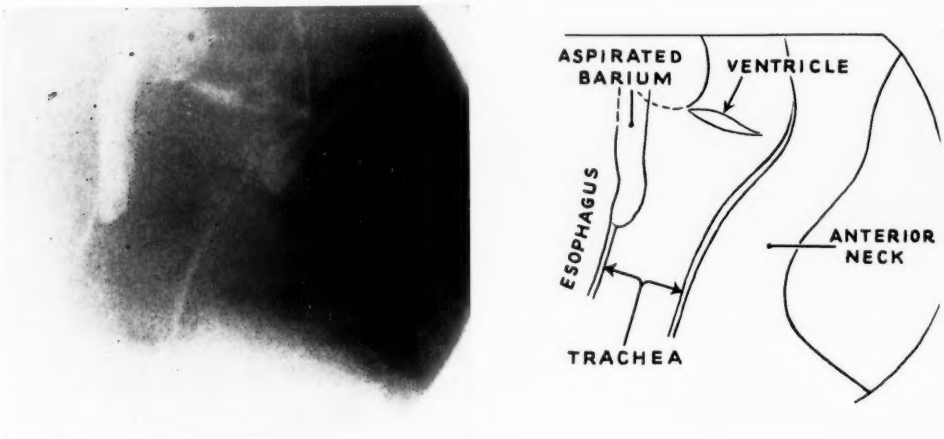

FIG. 5.

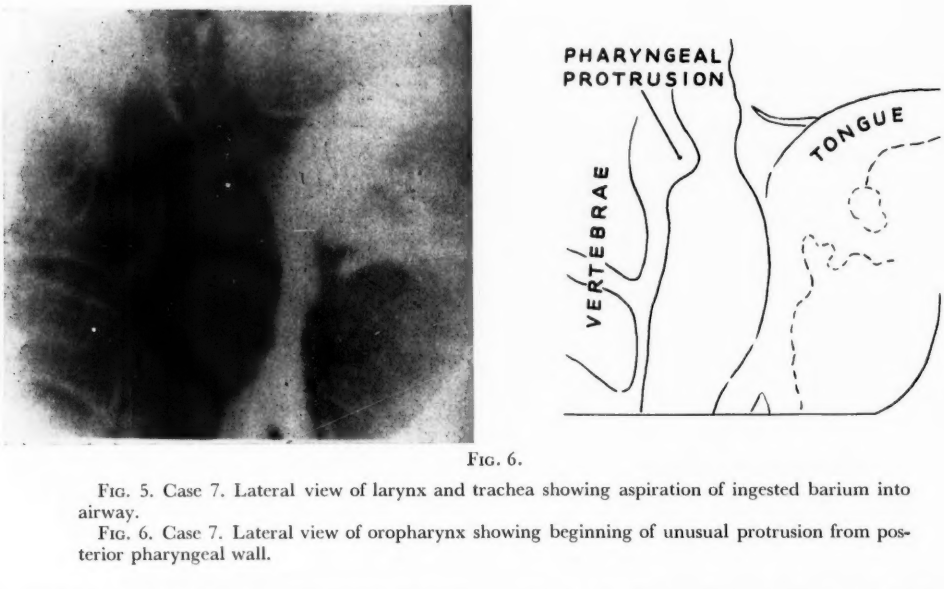

FIG. 6.

FIG. 5. Case 7. Lateral view of larynx and trachea showing aspiration of ingested barium into airway.

FIG. 6. Case 7. Lateral view of oropharynx showing beginning of unusual protrusion from posterior pharyngeal wall.

ponent of a reflex arc has resulted in failure of appropriate reflex closure of protective sphincters. The fact that movement of the remaining—right—half of the hyoid bone is so little impaired is of interest in itself, explaining roentgenologically an observation which has been made surgically, namely that one-half of the hyoid bone can be removed with very little effect upon function. The remaining half is seen to function normally despite the loss of its mirror image. The surgical detachment of anterior components of superior and middle constrictors has resulted in peculiar shapes seen in the lateral roentgenogram, probably representing the contraction of unattached muscle masses. The moderate interference with pharyngeal transport of bolus which is seen may be a result of structural alteration of the pharyngeal constrictor musculature, or it may be a function of the fact that escape via the nasopharynx occurs. The observation that elevation of the larynx is accompanied by marked deviation toward the left, the side operated upon, provides interesting demonstration of the rotatory effect of the intact opposite, right, thyropharyngeus portion of the constrictor muscle. It produces this deviation because it is unopposed by its left-sided counterpart which has been surgically removed (cf. Kirchner, 15).

FIG. 7. Case 7. Lateral view of swallowing, a few frames later than Figure 6, showing further increase in the peculiar pharyngeal protrusion.

Conclusions. (1) Roentgenologic evidence is presented of the manner in which loss of airway protective reflexes can result from unilateral ablation of the superior laryngeal nerve. (2) Unilateral surgical resection of the components of the faucial and constrictor musculature results in impairment of pharyngeal transport mechanisms, manifested by poor clearance of the radio-opaque material. (3) Detachment of anterior portions of constrictor muscles may result in peculiar protrusions from the posterior pharyngeal wall which can be seen in the lateral roentgenogram.

CASE 8. M. H., a 36 year old white female, was found in June of 1958 to have an epidermoid carcinoma of the left posterior portion of the tongue and vallecula with involvement of adjacent cervical lymph nodes on the left side. After preoperative irradiation, surgical resection was carried out. This consisted of radical dissection of the left side of the neck, extended to include detachment of all muscles from the left hemihyoid and resection of this structure. The pharynx was entered through a lateral pharyngotomy approach, and wide, deep local excision of the primary tumor was carried out, including portions of left genioglossus and hyoglossus. It was possible to spare the epiglottis, and care was taken to avoid damage to the superior laryngeal nerve. The left digastric muscle was excised. It was possible to close the operative defect primarily, after which uneventful healing occurred. Temporary tracheotomy and gavage feeding were utilized, but the patient regained good swallowing and airway function promptly.

Clinical status. Within a month the patient was able to eat most foods, maintaining her weight at a stable level. There was only minimal alteration in speech.

Cineradiographic findings. In June 1958, a preoperative study of deglutition was carried out which failed to show any detectable effect of the tumor itself upon swallowing function. There was a suggestion of retention of barium in the biopsy site. The epiglottis was well visualized, particularly in the anteroposterior view and seen to turn downward symmetrically as the bolus passed.

Upon postoperative examination in July 1958 (5 weeks after operation), conveyance of the barium from mouth to pharynx is seen to occur with minimal difference from the preoperative study, except for a suggestion that greater effort is required and that more movements are necessary to achieve evacuation of bolus from mouth. Palatoglossal (faucial) closure is competent.

There is minimal impression of slight dyskinesia in conveyance of bolus through the pharynx, and clearance is satisfactory. The anteroposterior view shows marked asymmetry of the epiglottis, with the left side turning down far more than the right. The asymmetry is presumably a result of the surgical resection. There is minimal vestibular intrusion which clears promptly. Movements of the remaining, right, half of the hyoid are within normal limits except for slight lateral rocking.

Interpretation. It is of interest to note how slight is the effect upon conveyance or faucial closure of resection of a considerable portion of posterior half of tongue on one side plus half the hyoid bone.

At least 10 muscles attach to each half of the hyoid bone. It is surprising to find that removal of this much of the bone results in so little effect upon the pharyngeal phase of swallowing. Apparently the intact contralateral half is able to participate adequately in the necessary motions.

Conclusion. Loss of one lateral half of the hyoid bone with detachment of all its musculature has minimal

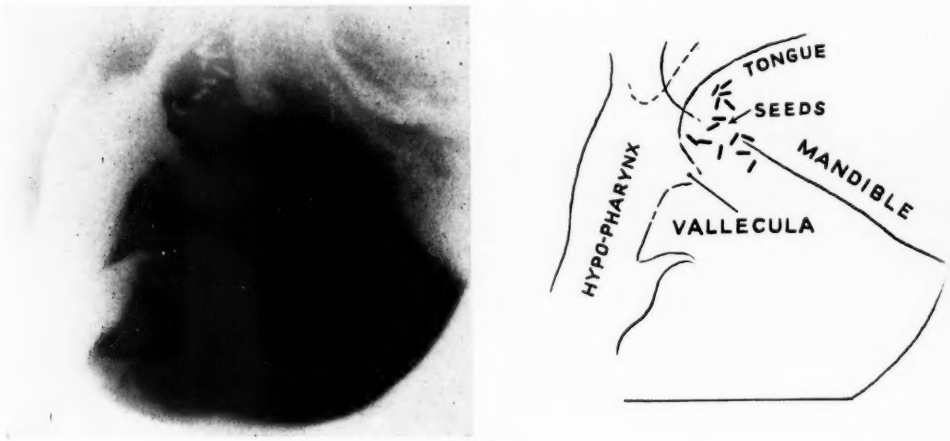

FIG. 8.

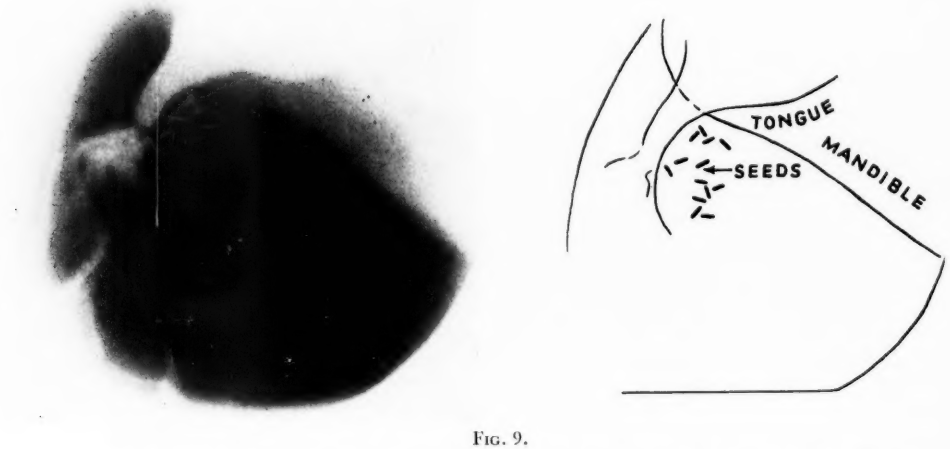

FIG. 9.

FIG. 8. Case 9. Lateral view of hypopharynx during swallowing with radon seeds outlining position of posterior tongue.

FIG. 9. Case 9. Ten frames after Figure 9, with radon seeds showing the rollback motion of posterior tongue.

effect upon either oral or pharyngeal phases of swallowing.

CASE 9. S. J., a white male, was 55 years of age when he developed a carcinoma of the right posterior tongue with involvement of adjacent cervical lymph nodes in September 1958. Treatment was begun with external irradiation directed to the primary tumor, and, in November 1958, operation was carried out. A radical dissection of the right side of the neck was done plus resection of the right hemihyoid and lateral pharyngotomy, through which radon seeds were implanted into the tumor in the posterior part of the tongue. The superior laryngeal nerve was preserved. Direct closure was carried out and primary healing resulted.

Clinical status. The postoperative course was uneventful and the tracheotomy was maintained for only a short period. Good swallowing and satisfactory speech are present.

Cineradiographic findings. In the preoperative examination in September 1958, it was seen that the barium column was diverted in its descent away from the tumefaction in the right posterior tongue. No other abnormalities were detected.

Upon postoperative examination in December 1958, little change in the observable dynamics of

FIG. 10. Case 10. Anteroposterior view of pharynx showing marked paretic dilatation of right pyriform sinus.

swallowing has resulted from the surgical intervention. The amplitude of motion of the remaining hemihyoid has been moderately reduced. The radon seeds provide clear demonstration of the movements of the posterior part of the tongue in the oral and pharyngeal phases of swallowing. It is possible to visualize the manner in which the tongue is first depressed forward to accommodate the bolus and then rolls backward and downward to participate with the pharyngeal musculature in providing the *vis a tergo*. Progression through the pharynx is satisfactory except for penetration of a small amount of barium into the larynx.

Interpretation. The surgical sacrifice in an operation of this extent has had little effect upon function. It is not possible to state the significance of the reduction in amplitude of hyoid movement. Of considerable interest is the direct demonstration of the manner of participation of the posterior part of the tongue in transport of bolus. Previous observations limited to visualization of the barium column itself have not provided a clear picture of the movements of the musculature of the posterior part of the tongue in swallowing, but in this patient the implanted radon seeds demonstrate clearly the downward thrust which the tongue, acting with the constrictors, can provide.

Conclusion. Radiopaque markers in the posterior portion of the tongue demonstrate a posterior and downward thrust of this structure, a movement which contributes to pharyngeal transport of ingesta.

CASE 10. B. P., a white male, was 62 years old in 1955 at the time an epidermoid cancer of the retromolar region of the right side of the tongue developed, involving the adjacent buccal mucosa and the anterior pillar. The primary tumor was successfully controlled by irradiation, but 9 months later, in 1956, a large right midcervical lymphatic metastasis developed. Because of this finding, a radical dissection of the right side of the neck was carried out, with moderate difficulty in separating the 6 centimeter diameter mass from the carotid vessels and from the pharynx, necessitating considerable dissection in this area. It is presumed that there was sacrifice of vagal branches innervating parts of the middle and inferior constrictor muscles. The right digastric and stylohyoid muscles were included in the resection.

Clinical status. The immediate postoperative recovery was uneventful, but 6 months later the patient was readmitted for what was thought to be recurrent cancer. He was having great difficulty in swallowing and had lost 40 pounds of weight. Careful studies failed to confirm the impression of recurrence of tumor, and it was found that the dysphagia was due to poor emptying of the pharynx. The swallowing difficulty improved on conservative treatment, and he was able to regain much of the lost weight. A complaint persisted, however, of a feeling of a lump in the lower portion of the throat during swallow, and in 1958, cineradiographic studies of deglutition were done.

Cineradiographic findings, March, 1958. There is seen no impairment of the transport of bolus through the mouth or faucial arches. Motions of the tongue are normal as judged by their visualization during the production of speech sounds.

There is marked impairment of conveyance of barium through the pharynx, based chiefly upon poor emptying of the right pyriform sinus. This structure fills to a larger size than its counterpart and the bolus remains within it over the course of many seconds, gradually emptying. When barium reaches the cricopharyngeal sphincter, it passes through normally and is carried down the esophagus in the usual

FIG. 11. Case 11. Lateral view of hypopharynx showing manner in which the radon seeds permit visualization of the movements of the pharyngeal wall during deglutition.

manner. Despite the sizable pharyngeal retention, there is only minimal laryngeal intrusion. Movements of the hyoid bone are not abnormal.

Interpretation. It is not surprising to find that the sacrifice of one digastric plus the stylohyoid results in no detectable effect upon the oral phase of swallowing.

The retention seen in the pyriform sinus is similar to that seen in certain patients having neuromuscular dysphagias based on cerebrovascular lesions. Apparently denervation of limited segments of the constrictor musculature results in significant impairment of function, which may lead, as in this patient, to severe dysphagia and malnutrition, a clinical picture which may suggest recurrence of tumor. Despite the pyriform sinus retention of barium, significant laryngeal intrusion does not occur, because satisfactory protective mechanisms persist.

Conclusions. (1) After extended radical surgery of the neck, even though the pharynx has not been entered, functionally significant motility disturbances of deglutition may result if segments of the lower constrictor musculature are denervated. (2) Such motility disturbances may be associated with considerable retention of ingesta in a pyriform sinus. Whether aspiration into the larynx occurs depends partly upon the integrity of its sphincter mechanism, and also upon the amount of retained material in the hypopharynx when restitution of the airway takes place at the end of swallow (cf. Kirchner, 14).

CASE 11. J. S., a white male, was 73 years of age when his problem began in 1955 with a carcinoma of the left epilaryngeal area with involvement of adjacent cervical lymph nodes. Surgical treatment was refused so that irradiation therapy was employed, both by external means, with temporary control of the tumor, and subsequently with interstitial implantation of radon seeds. These were placed in the left lateral pharyngeal wall at the arytenoid level, August 1957.

Clinical status. Complete control of the tumor was not obtained, but fair palliation was achieved, so that at the time of cineradiographic study in December of 1957 the patient was able to swallow reasonably well. His subsequent course was one of progression of the tumor necessitating tracheotomy in February of 1958. Death resulted from hemorrhage in April 1958.

Cineradiographic findings, December 1957. A filling defect is seen attributable to the tumor mass which is outlined also by the radon seeds implanted within it. Hyoid movement is of normal range. Most impressive is the extent of linear ascent of the pharyngeal wall itself as indicated by the motion of the radon seeds. The vertical ascent is greater than the height of a vertebral body.

Interpretation. The downward peristalsis component of pharyngeal propulsion is well accepted, but the second component, that of upward movement of the pharynx, has been difficult to demonstrate in the human. Negus has described this in terms of comparative physiology as an engulfment. It is possible to infer such an action from indirect observation of the hyoid and larynx and from the course of the radio-opaque bolus, but in this patient the radon seeds serve as markers to permit direct observation of the phenomenon.

Conclusion: In the human there is demonstrable, by means of radio-opaque markers in the pharyngeal wall, a definite vertical ascent of this wall during swallowing, corresponding to the engulfment movement previously described by Negus. This is seen to be equal at least to the height of one cervical vertebra.

ORAL PHASE

Discussion. Study of this group of patients results in some impressions regarding normal

and abnormal swallowing. Normal transport of ingesta from the mouth is achieved by a peristalsis-like stripping wave in the tongue, pressing against the palate and pushing the bolus forcibly posteriorward. The force of this propulsive mechanism is dependent upon two factors: (1) a tongue which is sufficiently intact to fulfill this function and (2) an intact musculoskeletal mylohyoid sling which can provide the upward thrust which is transmitted through the turgescent tongue to the palate. The upward diaphragm-like action of the sling may be defunctionalized not only by its complete removal but also by ablation of one-half of the muscle, or by removal or disruption of its skeletal support. The effect of denervation of the mylohyoid was demonstrated by Meltzer in the dog. The role played by gravity in the oral phase of swallowing will vary with position and with the adhesiveness and cohesiveness of the material being swallowed.

These patients, with varying degrees of interference with these mechanisms, provide some information as to the relative importance of the various components, briefly summarized in the next paragraph.

Case 2 (A. G.) has undergone partial defunctionalization of the mylohyoid sling but is able to convey adequately small boluses presumably because styloglossus and palatoglossus muscles are still able to provide some upward thrust of the tongue against the palate. Case 3 (A. M.), whose ablation of mylohyoid has been more extensive, displays similar compensation for the loss. Case 1 (J. O'C.) has lost more of the tongue than of the mylohyoid. His compensation is partly dependent upon repetitive camlike movements of the tongue remnant. Case 5 (P. S.) has lost an entire half of the sling, and his efforts to evacuate the mouth depend upon compensatory extension of the head and neck. In Case 4 (G. M.) a similar amount of the sling has been resected, resulting in an effortful oral phase with attempts to achieve transport by vigorous tongue movements. Case 6 (N. S.) has the most severe alteration of oral musculature. His adjustment consists of the virtual elimination of the oral phase of swallowing, in which ingesta are poured through the nonfunctional mouth directly into the pharynx. Case 8 (M. H.) demonstrates that unilateral hyoid loss has little effect upon swallowing.

Conclusions. These studies confirm in the human being what has long been known in the dog, namely that the mylohyoid is an important component of the oral phase of swallowing. Its optimal function requires an intact tongue to transmit the force of its upward thrust. When there is interference with the integrity of the musculoskeletal mylohyoid sling, the tongue is able to accomplish oral transport of small volume boluses. When surgical interference affects the tongue to a greater extent than it does the mylohyoid, compensations occur which have been described. When both mylohyoid and tongue are significantly defunctionalized, the first or oral phase of swallowing may cease to be a functionally separate component of deglutition.

PHARYNGEAL PHASE

Discussion. From the study of these surgically altered patients, certain impressions can be derived regarding the pharyngeal phase of swallowing. These will be considered separately under various categories.

Faucial Closure.—In 2 of the patients, data are available as to the dynamics of palatoglossal closure, the mechanism by which the oral cavity is closed off from the pharynx. Case 1 (J. O'C.), despite the defunctionalization of much of the anterior portion of the tongue, still retains a critical functional volume of the posterior part of the tongue to achieve competent closure. Case 6 (N. S.), on the other hand, has lost such a volume of functioning posterior portion of the tongue that he cannot effect a satisfactory seal. It appears, then, that competent palatoglossal closure requires not only functioning faucial pharyngeal elements, but also the support of a lingual component.

Case 7 (F. S.) has lost an amount of

faucial-palatal musculature sufficient to cause severe speech disability, with inability to control nasality. In the act of swallowing he is unable to avoid nasopharyngeal regurgitation of ingesta.

Pharyngeal conveyance.—There has been insufficient attention paid in writings on deglutition to the role of the tongue in pharyngeal transport. Some of the accounts do describe a rollback *vis a tergo* function in conveyance through the fauces, but the action seems to go beyond this. Ardran (4) has described an apparent compensatory role of the tongue in bulbar polio patients with paralysis of pharyngeal constrictors. In the present study, 2 of the patients, Cases 4 (G. M.) and 5 (P. S.), have undergone surgical procedures primarily of the oral cavity but with sufficient alteration of lingual kinetics to produce marked alteration in the efficiency of pharyngeal conveyance. The interpretation is that the downward wave of the constrictor muscles must be supplemented by some anterior component, which only the tongue can provide. A degree of compensation for this loss is seen in Case 6 (N. S.) in whom repetitive small waves replace the usual single major wave.

Kramer and associates have studied the action of the pharyngeal constrictor muscles in normal patients and patients with neuromuscular disorders both roentgenologically and manometrically, with a resultant understanding of the action of the constrictors. The patients in this study demonstrate further interesting facets of pharyngeal deglutition. Case 11 (J. S.) shows, with radon seeds in the pharyngeal wall, how extensive is the vertical engulfment portion of pharyngeal movement. Case 10 (B. P.) illustrates the severity of disability which may result from unilateral denervation of a relatively short segment of the constrictor musculature. Case 8 (M. H.) demonstrates that loss of half the hyoid bone results in negligible effect upon swallowing. This is of interest in view of its extensive muscular attachments, including the middle constrictor. Case 7 (F. S.) also is seen to have a good range of movement of the remaining half of the hyoid bone. These findings raise questions as to the role of the hyoid in the human. The latter patient shows, in addition, the effects upon propulsion of unilateral resection of a portion of the superior constrictor. The accompanying abnormal bulges seen could be a source of roentgenologic confusion. Such unusual protrusions have been seen also at lower levels in 1 patient after laryngectomy.

Airway protection.—Reference was made in the introductory portion of this paper to the complex set of mechanisms concerned with protection of the airway from aspiration of ingesta. The relative importance of the various components is not known. The role ascribed to the epiglottis, for instance, has varied with different accounts. In one authoritative source the chief factor in closure of the laryngeal opening during swallowing is said to be the drawing upward and forward of the larynx under the protection of the tongue. From the study of the abnormal patients here reported it is possible to reach some conclusions regarding mechanisms of airway protection. These are considered under several categories.

The patients studied have had varying degrees of interference with the structures supporting and moving the hyoid-larynx column. Cases 8 (M. H.) and 7 (F. S.) have each had resection of one-half of the hyoid bone with minimal resultant effect upon movements of the remaining half, indicating that an intact hyoid is not a prerequisite for adequate movement of the hyoid-larynx column. Case 5 (P. S.) has had resection of a hemimandible with negligible effect upon hyoid movement, demonstrating that loss of one-half the mylohyoid and one geniohyoid does not appreciably influence the manner of hyoid travel. Similarly, Case 1 (J. O'C.) shows little effect after section of both geniohyoids. Case 2 (A. G.) with more extensive resection of anterior mandible has as a result lost the forward component of hyoid travel, but has no problem in airway

protection. With the more extensive loss of both horizontal mandibular rami and the attached musculature in Case 3 (A. M.) the hyoid bone has lost all of its upward-forward movement. This finding confirms the impression that anterior submental muscles are responsible for some of the upward-forward swing of the hyoid. Despite this restriction of motion the larynx still ascends to the level permitted by the nonrising hyoid, and there is no vestibular intrusion of barium. In the patient with the most extensive resection, Case 6 (N. S.), essentially the entire mandible is gone as well as the hyoid bone. There is seen minimal ascent of the larynx during swallowing, and yet airway protection is adequate. Considering these patients as a group, the following conclusions are reached: (1) Upward movement of the hyoid-larynx column is dependent partly upon pharyngeal musculature, probably including the variable stylopharyngeus. (2) The forward component of movement is dependent upon the geniohyoid muscles. (3) Satisfactory deglutition (at least of liquids) is possible with no forward motion of the larynx and with minimal upward movement, provided that the intrinsic protective mechanisms are intact. These findings raise a question as to the validity of the traditional concept that airway protection is achieved by the larynx being drawn upward and forward under the shelter of the tongue. Ardran (3) also has demonstrated that in the so-called "trick-drinkers," who can down large volumes of beverage rapidly, swallowing can occur without laryngeal ascent.

There is fairly prevalent acknowledgement that the epiglottis does not play a critical role in preventing the ingress of ingesta into the larynx. The studies here reported add little to what is already known about this structure, which Pressman states should be considered as a part concerned in lower animals largely with olfaction. The movement of the epiglottis is seen inconstantly in the patients in this study, sometimes inverting and sometimes not. Of particular interest are the findings in Case 8 (M. H.), in whom the preoperative cineradiograph shows in the anteroposterior view the epiglottis symmetrically turning over. The postoperative study demonstrates marked deformity and asymmetry of the epiglottis, but there is no laryngeal intrusion of barium. One may conclude that the epiglottis plays a role in deflecting the ingesta down the lateral food channels, but that its role is not an indispensable one.

The importance of efforts to avoid injury to the superior laryngeal nerve has been mentioned by Martin. Two of the patients, Cases 7 (F. S.) and 5 (P. S.), in the present series have suffered damage to this nerve. In both of them significant difficulties resulted, and the roentgenographic studies visualize the intrusion into the larynx of barium despite seemingly intact motor mechanisms for protection. This observation demonstrates the manner in which failure of airway protection occurs on the basis of a loss of the sensory component of reflex arcs.

Penetration of cricopharyngeal sphincter. —There were no significant findings on this aspect of swallowing. One of the open questions in the physiology of deglutition concerns the relationship of laryngeal ascent to opening of the sphincter. Among the patients in this series were 2 in whom larynx ascent was minimal, but in whom there was noted no associated impairment of passage through the cricopharyngeal segment (cf. Kirchner, 14).

Conclusions. The ability to separate the oral cavity from the pharynx as part of normal swallowing requires not only functional anterior faucial (palatoglossal) elements, but also a critical volume of functioning posterior tongue. In patients lacking these elements there may cease to be a separation between the voluntary oral phase of swallowing and the pharyngeal phase. The posterior portion of the tongue plays an important part not only in the buccal-faucial transport of bolus but in the pharyngeal portion as well, where it acts in a complementary role to the constrictor musculature. There is in the human being definitely

a vertical (engulfment) component of movement of the pharyngeal constrictor musculature. Defunctionalization of even short segments of this musculature can result in significant disability in the act of swallowing. This finding indicates the desirability of preserving whenever possible during operation the motor pharyngeal branches of the vagus nerve. Anterior detachment of the constrictors may produce peculiar filling defects visible by roentgenography on the posterior pharyngeal wall. After surgical operations upon the upper aerodigestive tract, patients may lose to varying degrees the structures which support and accomplish the forward elevation of the hyoid-larynx column normally seen in swallowing. Some of such patients may experience considerable difficulty with inadvertent aspiration of ingesta, as reported by Edgerton. Other patients, however, will retain adequate protection of the airway against aspiration, for reasons which are not clear. The findings on the patients reported in the present study suggest that the intrinsic laryngeal mechanisms of protection are of more importance than elevation of the hyoid-larynx column. Adequate function of these protective mechanisms requires intact sensory innervation via superior laryngeal nerves. It is important, whenever possible, that the integrity of these nerves be preserved during operations.

SUMMARY

1. Cineradiography with image intensification provides a suitable method for the study of the alterations in oropharyngeal function which occur after surgical procedures performed upon the upper aerodigestive tract.

2. From a group of 11 patients so studied certain impressions can be derived regarding both normal and abnormal function.

3. Evidence is presented relating to the reciprocal role of the tongue and mylohyoid muscle in the oral stage of swallowing.

4. The contribution of the posterior portion of the tongue to competency of faucial closure is demonstrated.

5. When there is sufficient alteration in the posterior part of the tongue component of faucial continence, there may cease to be a separate oral phase of swallowing, the mouth then serving only as a passive conduit.

6. The complementary role of the posterior portion of the tongue to the pharyngeal constrictors in the pharyngeal phase of swallowing is clarified.

7. The engulfment action of the pharyngeal constrictors is demonstrated.

8. Evidence is presented as to the relative importance of ascent of the hyoid-larynx column as opposed to intrinsic sphincteric closure of larynx in airway protection during swallowing.

9. The importance of the superior laryngeal nerve and the motor pharyngeal branches of the vagus in deglutition is demonstrated.

10. In human deglutition, as in other body functions, there is a wide margin of reserve in which compensations for impairments can occur.

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A CONSIDERATION OF THE PROPER SURGICAL APPROACH FOR SUBSTERNAL GOITER

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THYROIDECTOMY ordinarily is thought of as being accomplished by the standard cervical approach through a so-called "collar" incision. Occasionally, a substernal goiter may appear too large for this type of removal because of the rigid aperture forming the exit from the mediastinum, in which case the surgeon may be tempted to split the sternum to complete the operation. Clagett repeatedly has pointed out that the trachea deviates from its anterior position as soon as it enters the mediastinum, so that splitting of the sternum may not provide the ideal exposure sought. In such a situation, he prefers lateral thoracotomy for those masses appearing to lie entirely within the thorax, especially if no cervical attachment can be demonstrated.

It is to be expected that in any survey of this type many thoracic tumors included will have been unknown factors for which the thoracic approach was the only feasible way to establish the diagnosis. In addition, certain patients will have had one or more cervical thyroidectomies and will have presented themselves again with a substernal mass not at all certain to be thyroidal in origin. The mere presence of a scar of the collar type does not prove the thyroidal origin of the substernal mass, although it is at least presumptive evidence. The newer diagnostic aids, however, should make proper diagnosis possible now in doubtful cases.

We have long believed that removal of a substernal goiter via the cervical approach, when that is possible, results in a simpler, perhaps less risky, definitely less expensive convalescence for the patient. The increasing frequency of reports on the thoracic approach to these goiters led us to investigate our own situation to see whether a trend is developing.

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REVIEW OF LITERATURE

Long ago, Pemberton presented technical features of thyroidectomy which we have applied to good advantage through the years. He reported that among 4,006 thyroidectomies, 542 (13.5 per cent) of the goiters were of the substernal type. Of these, 25 (or 0.6 per cent of his series) were entirely within the thorax. Pemberton was among the first to suggest that the cervical approach be employed in these cases whenever feasible. He demonstrated that the substernal mass could be morcellated and the deepest portion of the goiter withdrawn piecemeal, so that the encapsulated remainder could be extracted gradually from its deep position. His method stressed local anesthesia, which often permitted the patient to cough at the command of the surgeon to facilitate delivery of the deep portion of the mass. Considerably later, Ellis, also from the Mayo Clinic, writing with Good and Seybold, presented a somewhat different view—that of a surgeon interested primarily in thoracic diseases. He pointed out, however, that masses in the superior mediastinum might be approached through a cervical incision with additional splitting of the sternum as occasion demanded. Without splitting of the sternum, the thoracic surgeon might prefer thoracotomy to the cervical route because of the possibility of trauma to the superior vena cava. Ellis believed that masses deep in the mediastinum and unassociated with a cervical goiter,

especially if thyroidectomy had not been carried out previously, should be approached by thoracotomy or at least by the "sternal split." The posteriorly placed substernal tumors seem to comprise the largest portion of this category.

Colcock favored the standard cervical approach whenever possible, adding that general anesthesia always should be employed and that tracheotomy might be an integral part of a large percentage of such operations. O'Malley and associates presented an excellent summary of this same problem with accurate illustrations and measurements of the substernal masses under discussion. They said that only rarely had they found it necessary to split the sternum, and that tracheotomy should be kept in mind when this much intervention is required. They agreed with Pemberton that morcellation of the mass with gradual or piecemeal removal to obviate thoracotomy was advisable in most instances. Like others, they stressed the lag in restitution of the mediastinum to normal following removal of the substernal mass. This they regarded as probably due to edema, and in some instances to hemorrhage.

Sweet gave special attention to the posteriorly placed masses and to that portion of the recurrent laryngeal nerve that is within the chest. He pointed out that the goiters which enter the posterior mediastinum lie between the recurrent nerve and the inferior thyroid artery. He, too, stated that almost without exception anterior intrathoracic goiters can be removed by the usual approach through the neck; and he argued for early removal because of the great increase of technical difficulty with growth of the goiter. He believed that the importance of anterior location as opposed to posterior location lay in the need to prepare for thoracotomy when attacking goiters in the latter situation.

Lindskog and Goldenberg also favored use of the cervical approach whenever feasible. They stressed the problem of differential diagnosis and the serious consequences to which certain mistaken diagnoses could lead. Of their 31 patients, only 2 had required supplementary incision through the superior medial part of the sternum and 1 other had undergone formal transpleural thoracotomy after preliminary cervical exploration with removal of a cervical adenoma. They emphasized that "there is an undesirable tendency among some surgeons with facility in thoracic surgery to abandon the simpler cervical approach to substernal goiter." Blades, writing with Adkins, was willing to approach these masses through whichever appeared the more feasible entry, but believed that the cervical approach would suffice in most instances. However, he argued against use of the sternum-splitting technique, and actually stated that this method should not be employed because frequently the postoperative pain is severe and infection of the wound may be serious. Also, he thought that morcellation of the substernal mass was not advisable. When necessary, he used anterior thoracotomy through the second or third interspace.

PURPOSE OF PRESENT STUDY

Having become aware of a certain tendency in recent years away from the well proved standard approach to the goiter of which part or all appears to lie in the intrathoracic region, and having felt, much as Lindskog did, that increasing interest in thoracic surgery might possibly lead to overemphasis of the thoracic approach, we have thought it worth while to re-evaluate our position and experience with respect to these alternatives. This article reports our experiences in the removal of substernal goiters by the cervical route on the one hand, and by the thoracic route, including the sternum-splitting method, on the other.

MATERIAL AND METHOD

From the records of the Mayo Clinic it was found that prior to 1950, in approximately 40,000 thyroidectomies, an approach other than the cervical was employed in only 17 instances. In the period 1950 to

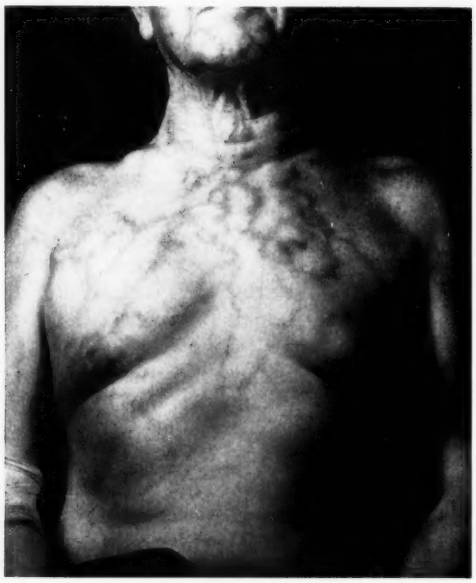

FIG. 1. Effect of obstruction of jugular system by substernal goiter (infrared photograph).

1956, inclusive, among 5,819 thyroidectomies the thoracic approach was employed 24 times. The records for this period of higher incidence were analyzed. When all factors were considered carefully, with review of thoracic roentgenograms and study of the surgical reports, we accepted 112 cases as true substernal goiter. That slight extension beneath the clavicles or marked enlargement in a superficial area did not suffice to categorize a goiter as a true substernal mass is implied by the fact that the instances classed as substernal amounted to only 1.9 per cent of all goiters removed in these 7 years. The history, the record of physical examination and all laboratory tests, the pathologic diagnosis, and the weight of the gland were available in every one of these cases.

TABLE I.—SYMPTOMS AND SIGNS OF SUBSTERNAL AND INTRATHORACIC GOITERS

Symptom	*Removed by cervical route (88)*	*Removed by thoracic route (24)*
Hyperthyroidism	14	1
Cyanosis	2	
Stridor	23	
Dyspnea		1
Dysphagia, slight		4
Hoarseness		1
Pain		3

We divided the 112 cases into two groups: the cervical-approach group, 88 cases in which thyroidectomy was accomplished through the standard collar incision; and the thoracic-approach group, 24 cases in which a lateral thoracotomy or the sternum-splitting technique was used.

FINDINGS

In the cervical-approach group of 88 patients, we found that the average age was 58 years with a range from 36 to 78 years. There were 67 women and 21 men, giving a ratio of more than 3:1. In 9 of these patients, the goiters were recurrent, a fact indicating that their previous thyroidectomy was of the cervical type, with retention of the substernal portion because of technical reasons or possibly because of oversight. Strangely, only 1 of these 9 patients was in a state of hyperthyroidism when first examined, and this patient at that time was experiencing a fourth recurrence in a 34 year period.

In the thoracic-approach group of 24 patients, the average age was 52 years with a range of 30 to 70 years. There were 15 women and 9 men, giving a ratio of 1.7:1.0. In this group, 8 patients had undergone cervical thyroidectomy previously, and thus their goiters were recurrent. In 1 of them the cervical goiter had been removed here and the intrathoracic portion had been discovered at that time; but as it was entirely separate from the cervical goiter, the surgeon presumed that the blood supply came from the chest and elected to deal with it separately. Two weeks after the cervical thyroidectomy, thoracotomy was employed for the removal of the intrathoracic mass. There had been some question of the status of the recurrent laryngeal nerve at the first operation; but at the second operation, employing an endotracheal tube, no difficulty was encountered.

SYMPTOMS AND SIGNS OF SUBSTERNAL GOITER

This discussion of the clinical findings will be confined to those of the thyroid region (Table I), as they are the ones with which the physician is most concerned and the ones which help most in deciding the surgical approach. Examination was greatly facilitated by having the patient drink liberal amounts of water during its course. Sometimes, also, the straining maneuver of Valsalva would cause a previously normal-appearing cervical region suddenly to disclose a rather obvious mass on one or both sides. Since the surgeon is intimately concerned with the presence or absence of a cervical goiter, the cervical findings seemed of paramount importance and they have been summarized for both groups in Table II, which plainly indicates that ordinary examination can fail to disclose small adenomas. Once the roentgenologic findings were at hand, however, the physical examination of the cervical region was intensified and repeated by multiple observers; and the findings listed are the final record.

It should be mentioned in this regard that scars from thyroidectomy and histories of one or more previous thyroidectomies were valuable factors, in that the presence of such evidence increases the probability that the mass is of thyroidal origin. Sometimes venous obstruction was a prominent factor, and occasionally the physical signs of it were prominent. Photographs made with the infrared technique could offer striking evidence (Fig. 1).

DIAGNOSIS

In addition to the features already outlined, we learned that the roentgenographic findings were of primary importance in both of these groups. Frequently, the routine thoracic roentgenograms suggested mediastinal widenings which called for further study. In such instances the patients were returned to the Section of Roentgenology, where fluoroscopy usually demonstrated that the mass moved upon swallowing. In several cases of both groups, however, the mass was of such size and so tightly wedged in the mediastinum that it could not be seen to move with swallowing, and its exact nature was demonstrated only at surgical exploration. A very common finding in both groups was marked deviation of the trachea, which was readily disclosed roentgenologically (Fig. 2); and in some individuals there was obvious compression of the tracheal cartilage also. Calcification in the mass led the roentgenologists on several occasions to conclude that the tumor involved the thyroid gland, although this judgment, of course, is not invariably right.

a b

FIG. 2. Deviation of trachea and esophagus due to substernal goiter located in upper posterior mediastinum; goiter removed via cervical route. a, Anteroposterior view. b, Lateral view.

In the majority of cases in which the cervical approach was employed, the diagnosis was made in the usual manner in the regular diagnostic departments. In the other group, the majority had been referred to that diagnostic section particularly concerned with diseases of the thorax, as thoracic roentgenograms had disclosed what was thought to be a thoracic tumor of other

TABLE II.—THYROIDAL FINDINGS ON PALPATION

Findings	*Cervical-approach group*	*Thoracic-approach group*
Not palpable	10	13
One or both superior poles just palpable	23	11
Small goiter felt	39	
Large goiter felt	10	
Not stated	6	
Totals	88	24

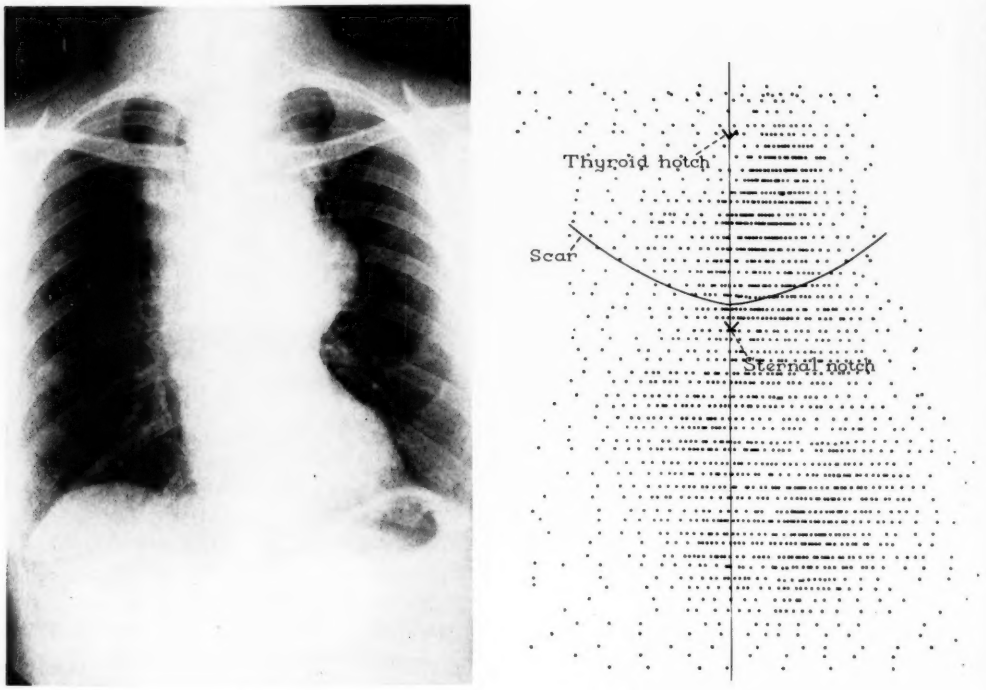

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FIG. 3. a, Substernal mass of unknown origin. b, Gammagraph after administration of radioactive iodine proving mass to be thyroid.

than thyroidal origin. Here, alternative diagnoses were thymoma, lymphoma, enterogenous cyst, and granuloma. Thoracic aneurysm was considered in several cases, as were neurofibromas and, in 1 case, pharyngoesophageal diverticulum.

It might seem that radioactive iodine studies would be of great importance in deciding whether a given tumor is actually of thyroidal origin. The isotope was employed in many of these cases, but it appears that other diagnostic criteria had been sufficient in most and the gammagraphic survey was merely contributory evidence. In 1 case of the cervical-approach group, radioactive iodine was of great value in reaching the final conclusion (Fig. 3). In all but 2 cases of the thoracic-approach group the proper diagnosis finally was achieved by a combination of the evidence from radioactive iodine with the other criteria already discussed. To us, it appears that only 2 patients in whom diagnosis was unknown were finally operated upon, and we believe the use of the thoracic approach in these instances was definitely correct. In 8 other cases of the thoracic-approach group there had been previous cervical thyroidectomy, and we concede that quite possibly the thoracic approach was the only logical one under these circumstances. In the majority of the remaining cases, the tumors were of such size that it

TABLE III.—SITE OF ORIGIN OF SUBSTERNAL MASS

Site	*Cervical-approach group*	*Thoracic-approach group*
Isthmus	2	
Right lobe	22	20
Left lobe	37	
Both lobes and isthmus	18	4
Not specified	9	
Totals	88	24

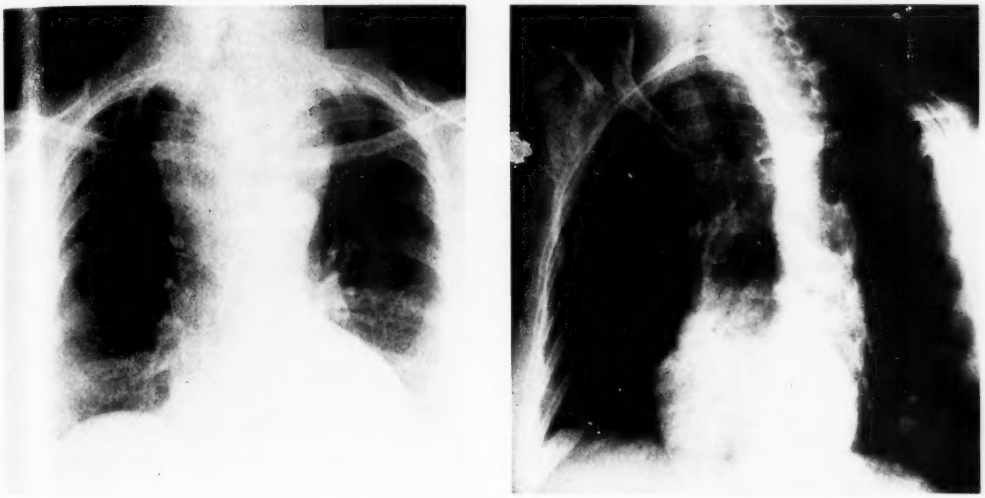

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FIG. 4. Large substernal goiter removed readily via cervical route. a, Anteroposterior view. b, Oblique view.

appears the surgeon preferred to start with a thoracic approach for that reason alone.

CHOICE OF METHOD

Apparently, in cases which included previous cervical thyroidectomy but afforded no current abnormal thyroidal findings in the neck, it was deemed preferable to approach a large mediastinal goiter mass by thoracotomy. The blood supply presumably would have been altered drastically by the cervical thyroidectomy. The problem of the blood supply assumes paramount importance when the thoracic surgeon discovers that the mediastinal mass he has just exposed is actually a substernal goiter which never has been dealt with surgically before. All of the blood supply still comes from the neck, and his technical difficulty may be great for that one reason. This may account for the recurrent laryngeal nerve injuries reported after approach by thoracotomy.

It is striking that in the thoracic-approach group the overwhelming majority of the abnormal masses arose from the right lobe of the thyroid gland (Table III). The danger of injury to the superior vena cava appears to have been minimized when the thoracic approach was used in these instances.

Although experienced surgeons realize that seemingly huge masses may well be extracted from above (Fig. 4), it was something of a surprise that the average weight of the cervical goiters was definitely greater than that of the thoracic specimens. The former group averaged 141 grams (range 30 to 775) and the latter 128 grams (range 31 to 395). Further, 14 specimens in the cervical-approach group weighed more than 300 grams, indicating that size alone does not necessarily prohibit use of the cervical approach.

The most decisive factor is location. If the uppermost portion of a substernal goiter appears roentgenologically to be no lower than the "jugular notch," removal can be accomplished by the cervical route.

COMPLICATIONS OF SURGERY

The difficulties experienced after operation were rather readily assessed and are perhaps best presented in Table IV. The most obvious complication—and one of

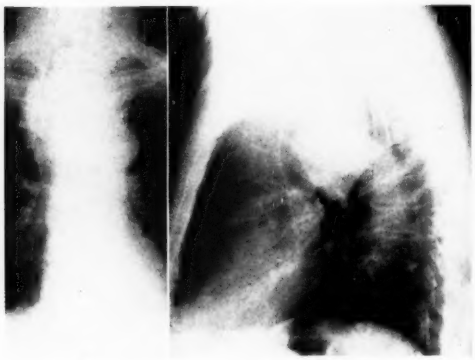

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FIG. 5. Substernal goiter with adenocarcinoma in the left lobe; goiter removed via cervical route. a, Anteroposterior view. b, Lateral view.

immediate concern to surgeon and patient alike—is paralysis of a vocal cord. It will be noticed that the paralysis was not bilateral in any case. Among the 7 instances in the cervical-approach group, 5 involved the right cord and 2 the left. In 1 case, 2 months were required for resumption of entirely normal function, and in another the larynx was found to be functioning normally when the patient was examined 1 year after operation. In 4 others, the recurrent nerve was demonstrated at operation in a very satisfactory fashion; and although these 4 patients have not undergone formal laryngeal examinations since dismissal from the clinic, because the nerve seemed intact and uncompromised it has been assumed that function returned in the course of time. In the seventh instance, the paralysis is assumed to be permanent.

TABLE IV.—COMPLICATIONS OF THYROIDECTOMY FOR SUBSTERNAL AND INTRATHORACIC GOITER

Complication	*Cervical-approach group (88)*	*Thoracic-approach group (24)*
Paralysis of vocal cord (unilateral)	7*	4
Temporary tracheotomy	2	0
Thrombophlebitis	1	1
Atelectasis		1
Pneumonitis		1
Pulmonary embolus		1
Osteomyelitis of sternum		1
Rate, per cent	11	37

*Two subsequently found to be normal, and 4 others thought to be temporary.

It is of interest that in the thoracic-approach group the vocal cord paralysis noted in 4 cases affected invariably the cord on the right side, just as five-sixths of the adenomas in this group affected the right thyroidal lobe. Paralysis was transitory in 2 of these cases, but in the other 2 definite paralysis persisted at the time of dismissal. Here it seems probable that actual trauma to the nerve occurred, but long term follow-up examinations in these patients' home areas were not directed particularly to the larynx, and we have no grounds for assumptions regarding the return of function in these cases.

The 2 cases that required temporary tracheotomy were of particular interest, for in the cervical-approach group the anesthesia most commonly was local, although in the majority of these operations routine mixtures of nitrous oxide and oxygen were administered during most of the procedure. In the first case, which was an instance of recurrent goiter, severe stridor developed at the end of the operation and tracheotomy was performed for that reason. The tube was removed a few days later. In the second case also the goiter was recurrent, the patient having had 3 thyroidectomies previously and yet again was observed with hyperthyroidism. This time the tracheotomy tube was retained during most of the convalescent period but then was removed without incident. In 1 special case, stridor and cyanosis were so extreme at admission that an emergency tracheotomy was required. Five days later, after preoperative preparation of the patient, the surgeon was able to proceed with thyroidectomy.

One patient of the cervical-approach group suffered thrombophlebitis, a complication not expected with this type of operation. This appeared on the fourteenth postoperative day, when the patient had been out of the hospital for a week. It responded to the usual conservative measures.

The atelectasis recorded occurred in the right lower lobe. In the case of pulmonary embolus there was extensive thrombosis of

the right subclavian vein after thoracotomy on the right. The osteomyelitis of the sternum was similar to that reported by other observers, a factor which has led Blades and Adkins and others to condemn the sternum-splitting approach. In this particular case, the osteomyelitis required curettage 1 month after the thoracotomy, and several months elapsed before healing was complete.

MORBIDITY AND MORTALITY

The average stay in the hospital for the cervical-approach group was 6 days. In this entire group only 1 blood transfusion was administered, this being 500 milliliters given during the operation. One patient required a return to the operating room on the day of operation for the insertion of a pack in the cavity to control persistent oozing. In contrast, the average stay in the hospital for the thoracic-approach group was 11 days, with range from 6 to 30. Obviously, the morbidity was that associated with a more major operation, of which the thoracotomy itself was a significant portion. It is estimated that the risk of trauma to the recurrent laryngeal nerve was at least twice that incurred with the cervical approach.

There was only 1 death in the entire group of 112 patients. This occurred in the thoracic-approach group. Unfortunately, permission for necropsy was not granted and the exact cause of death remains a matter of speculation. Review of the clinical record suggests coronary occlusion, although pulmonary embolism has been considered also.

PATHOLOGY

The usual report on the surgical specimen was that of "multiple, degenerating, colloid and fetal adenomas in a colloid thyroid." This report was rendered in approximately 95 per cent of all cases. Occasionally other features were added, such as calcification, hemorrhage, fibrosis, or hyaline changes. One patient had extensive hemorrhage within a large adenoma, and this apparently produced the sudden changes noted clinically with stridor, dyspnea, and hoarseness. In only 2 of the patients was thyroiditis of such degree as to be classified in a formal category. It is surprising to note that only 1 specimen revealed any evidence of malignancy; here the incidental finding within the adenoma was follicular adenocarcinoma (Fig. 5).

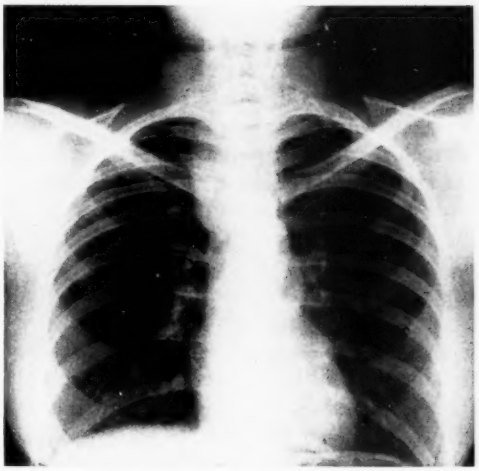

FIG. 6. Substernal goiter which was removed by thoracic route. Apparently, the cervical route might have been equally effective and somewhat simpler.

FAILURE OF SURGICAL EFFORTS

To the best of our knowledge, surgical failure occurred in only 1 instance. Here

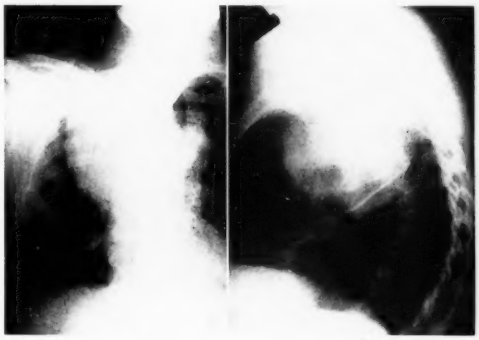

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FIG. 7. Substernal goiter that required thoracic approach for removal. a, Anteroposterior view. b, Lateral view.

was an extreme development of a substernal mass. The approach employed was the standard collar incision and the surgeon removed the cervical portion of the goiter, which weighed 390 grams. Below the sternum, just at the tip of the finger, he could palpate another mass that was completely separate from the thyroid gland and fixed to the chest wall. He was not able to remove this by the cervical route. After convalescence and complete healing of the wound a thoracic surgeon was consulted, who advised a sternum-splitting approach to remove the separate, isolated, but presumably thyroid, mass. The patient never has returned to have this part of the operation completed.

COMMENT

Properly conducted, the standard thyroidectomy can be a simple, safe, and completely effective operation. This applies even though the goiter is large and substernal (Fig. 6). The cervical approach permits complete control of the arterial and venous blood supply, accurate identification of the recurrent laryngeal nerves, and proper preservation of the parathyroid glands. We usually have employed local anesthesia supplemented during most of the operation with a mixture of nitrous oxide and oxygen. This method frequently allows the patient to co-operate during the operation by coughing and straining at command in order to help deliver the substernal mass into the cervical incision. In some instances morcellation of the mass with aspiration of its contents or even piecemeal removal of the central portion of the mass with a placenta extractor makes possible traction on the capsule of the goiter, eventuating in complete removal with no injury to surrounding structures.

Occasionally, marked tracheal deviation or excessive size of the substernal goiter leads us to employ general anesthesia administered by an intratracheal tube, although the morbidity postoperatively may be somewhat increased over that following the other method. We are prepared to extend the collar incision with a splitting of the sternum if indicated, but this almost never becomes necessary. Rarely, the posterior position of some huge substernal goiters may require thoracotomy (Fig. 7). This applies more especially to cases in which cervical thyroidectomy has been employed before and the current problem is a formerly overlooked or newly developed mediastinal tumor of thyroidal origin.

SUMMARY AND CONCLUSIONS

Modern methods of diagnosis are inadequate to identify properly the majority of unknown mediastinal masses without thoracotomy. Transthoracic thyroidectomy will continue to be necessary for certain huge substernal goiters. This approach may be required also for those recurrent goiters lying entirely within the chest and not convenient to a repetition of the cervical approach.

Surprisingly, large substernal goiters still may be removed via the standard cervical approach with a very low risk and a low morbidity rate.

As cervical thyroidectomy can be accomplished safely with a relatively uncomplicated and inexpensive convalescence, it is to be weighed seriously in a consideration of the surgical approach to any substernal goiter.

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LAUREL A. WEIBEL, M.D.

Footprints in the Snow

EDITORIALS

THROMBOSIS

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The natural history of thrombosis is essentially the natural history of the thrombus. —VIRCHOW.

THROMBOEMBOLISM continues to be foremost among the problems in medicine. Whether one considers it to be on the increase or decrease depends on whose statistics one chooses to accept. The diagnosis may be difficult, particularly in its more dangerous forms, before, at the time of, or even after a fatal embolism. Some of the more recent factors possibly contributing to its occurrence are the increased longevity of the population in general, the more involved diagnostic procedures, the extensive therapeutic measures now in use, the widespread use of intravascular infusions of many types and substances, and the tendency of the surgeon to more extensive exploration, resection, repair, and transplantation in all areas of the body.

Investigation in all of these fields goes on at an ever accelerating pace, and the results speak for themselves. Too often, however, success is short-lived, and a fatal embolus overshadows the promising therapeutic measure.

The cause of intravascular clotting is not known. A century ago Virchow suggested that the principal factors predisposing to thrombosis are: (1) local changes in blood vessel walls, (2) stasis, and (3) alterations in the coagulability of the blood. These precepts are still considered valid although their respective roles are far from being understood.

It is common knowledge that local trauma to or about a vessel may result in platelet thrombi and that these may form even in the presence of incoagulable blood. Such thrombi may develop, however, without propagation and without clinical signs of thromboembolism. The investigator who would produce thrombi in the experimental animal is all too aware of the difficulty in achieving this through local trauma to the vessel wall. How few of the many persons of all ages who sustain severe injury develop thrombosis! Infection and inflammation are considered factors in promoting intravascular clotting and, yet, how often they occur with no evidence of thrombophlebitis.

In support of the role of stasis as a factor, there are a number of reports of thrombophlebitis developing in the legs after long periods of sitting or of riding in plane or automobile. Yet, how much greater is the number of people who sit or ride under similar conditions and do not develop thrombophlebitis. Every medical student is taught that, while stasis is no doubt a factor in the development of thrombosis, blood trapped between two ligatures on a vein may remain fluid for weeks. On the other hand, when Wessler injected homologous serum into the antecubital vein of a dog and, 1 minute later, gently applied 2 clamps to a segment of the animal's jugular vein "a red clot forming a cast of the isolated segment routinely developed within 60 seconds." The fact that thrombosis is, for the most part, a localized process lends support to the suggested role of stasis and local vascular changes in the development of this condition.

It would appear then, that while stasis of blood and local changes in and about walls of blood vessels may be factors in the development of thrombosis, there must be other and perhaps more important adjunctive influences at work.

The normal physiology of blood coagulation is still poorly understood. Only a few of the steadily growing number of clotting factors have been isolated in even relatively pure form, and most are known only by specific activities measurable in isolated clotting systems. Since the normal physiology is poorly understood it follows that abnormal clotting states are even more difficult to define. Shortly after the turn of the century, Morawitz presented the concept that a substance known as prothrombin, in the presence of calcium and thromboplastin (tissue juice), is converted to thrombin, a powerful enzyme which subsequently converts fibrinogen to the insoluble gel, fibrin. Although this original concept, involving four factors, is still considered to be fundamentally true, it has been extended to include a number of additional factors. It appears now that thromboplastin is not only released as a result of tissue damage but actually may develop in blood itself through the interaction of certain plasma proteins and cellular components. Thus, antihemophilic globulin (AHG), plasma thromboplastin component (PTC), calcium, a substance from platelets (probably a phospholipid), and accelerator globulin (Ac-G) interact to form "intrinsic thromboplastin," which rapidly converts prothrombin to thrombin. Both thromboplastin and thrombin are effectively neutralized in plasma by direct inhibition as well as by actual destruction.

It appears reasonable to consider clotting as a delicately balanced dynamic process. Thus, although, even under normal conditions, a limited amount of clotting may occur continuously, various other factors prevent the excessive accumulation of the end products of this process both by limiting its rate and by removing the fibrin as it is formed. This fibrinolytic activity (plasmin) can be readily demonstrated in normal patients and may become excessive in various clinical states. There is evidence that the plasmin precursor, profibrinolysin (plasminogen) may be acted upon by a tissue activator as well as by an activator present in the plasma itself, thereby suggesting an active role of the vessel wall in fibrinolysis. In any given area, the condition of the vascular surface is apparently closely related to the balance or imbalance of the clotting mechanism. A positively charged surface such as glass accelerates clotting while negatively charged surfaces inhibit it. There is evidence that vascular endothelium is normally lined by negatively charged mucopolysaccharides to which class of substances heparin belongs. The role of various heparin antagonists in altering a negatively charged endothelium is still uncertain, but an important part has been ascribed to at least one factor, plasma thromboplastin component (PTC). The so-called Hageman factor and the recently described prephase activator (P.P.A.) may also be involved in this process.

Complex as the clotting mechanism may appear it is further complicated by the many influences upon it of modern living and of methods of diagnosis and therapy. Some of the factors reported to promote clotting are: stress, mental, emotional, or physical; shock; the lowering of body temperatures with the precipitation of cryoproteins; marked fall in blood pressure; alterations in gas tensions (oxygen, carbon dioxide, nitrogen); certain drugs such as the methylxanthines (caffeine, theobromine, theophyllin, aminophyllin), digitalis, certain antibiotics, narcotics, and sedatives (morphine, procaine, and demerol), and some of the tranquilizers; hormones such as the corticosteroids, stilbestrol, premarin, lutein, and gonadotropin derivatives, and adrenalin; fats, particularly those containing phospholipids and certain fatty acids.

Of particular interest is the fact that there are in the circulating plasma certain measurable proteolytic enzymes which are clot-

promoting. Of these, trypsin is one of the better known and may be, at least in part, responsible for the tendency to thrombosis observed in patients with carcinoma of the body or tail of the pancreas. More recently, an enzyme known to attack the ester linkage in certain synthetic substrates has been found to be elevated in patients with a history of thromboembolism as well as those with evidence of active intravascular clotting. Although the specific source of this enzyme activity is still uncertain, there is some evidence to indicate that it may be derived from one of the intermediate products formed during the development of "intrinsic thromboplastin." It is of interest that the activity of this enzyme is rapidly reduced as a result of prothrombin-depressant anticoagulant therapy, this reduction occurring more rapidly than the depression of prothrombin to the generally accepted therapeutic bracket of 10 to 30 per cent of normal. In patients on long-term anticoagulant therapy the esterase activity is found to be at extremely low levels.

It is likely that thrombosis in different patients is not the result of identical changes in their broad respective coagulation mechanisms. It is more probable that these changes come about as the result of alterations in a number of factors in each instance and that, while some of these alterations may be basically the same in all patients, in others they may be of a different nature.

While Virchow's triad still appears to be valid, of the three contributing factors, alterations in the coagulability of the blood would appear to be the most important. Furthermore, changes in the rate of blood flow and in the local state of the vessel walls may themselves be influenced by alterations in various coagulation factors.

Serious as are the consequences of intravascular clotting in surgical patients, a relatively small percentage of surgical procedures is complicated by this dread condition. Large numbers of patients of all ages are severely injured in many different ways without developing thromboembolism. Long periods of sitting or riding with legs dependent are not followed by thrombophlebitis in most patients. In many patients with severe varicosities of the saphenous system thrombosis never develops. And yet not a few people, many of them young, even teen-agers, may, without apparent cause or reason, experience recurring bouts of thrombophlebitis with or without embolic episodes.

The reasonable conclusion then, even in the present incomplete state of our knowledge, is that there are those of us whose clotting mechanism is improperly balanced so that, with proper triggering, the thrombotic process is set in motion. If this be true, the solution to the problem of thromboembolism is to be mainly through the elucidation of the changes responsible for this "thrombophilic state," the prevention of these changes, their early detection, and their neutralization once they have occurred.

What, then, can we as surgeons do to meet the problem of thromboembolism? Let us be sure that any involved diagnostic procedure is likely to yield information of sufficient value to be worth the possible risk of any physiologic changes it may produce. Since almost any therapeutic measure may be suspect as an influence, however slight, on the clotting mechanism, let us give careful thought to all forms of therapy before they are instituted. Let us be sure that every drug or contemplated infusion is likely to help the patient more than harm him; let us lose no blood that we can properly avoid losing; in our handling of tissues let us be gentle (in the words of one of my old teachers, "as gentle as a caress"); let us avoid, when possible, that "single unit blood transfusion"; in performing a laparotomy, let us put up with a little technical inconvenience if a thoracoabdominal incision is not really necessary. In a word, let us never lose sight of sound surgical principles, and expect the new necessarily to justify our violations of the old.

The use of anticoagulants is relatively new, scarcely 2 decades old, and opinion is still varied on its validity and safety. It

seems reasonable to assume that the effective treatment of thromboembolism will come through this approach. If some invesitgators can effectively and materially reduce the incidence of thromboembolic episodes, conflicting reports would appear to be a matter of methods of control, of practice, and of familiarity rather than of principle. Let us then study the methods of those whose experience indicates that they can successfully treat thromboembolism and, in most instances, prevent its recurrence. Let us familiarize ourselves with the proper use of heparin and one or perhaps two of the prothrombin-depressant drugs. Let us discover their properties, their advantages, and their defects, and let us insist on the best available laboratory methods for the control of their administration.

And in all surgical procedures, all medical procedures, diagnostic or therapeutic, in order to accomplish our objective let us disturb the normal physiology of the patient as little as possible.

Let us "be not the first by whom the new are tried, nor yet the last to lay the old aside."

SURGEONS: AGE, TRAINING, AND CREATIVITY

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PERUSAL of the literature of the medical sciences indicates that few surgeons have played an important role in the discovery of new principles in biology, diagnosis, or nonsurgical therapy. In fact, many contributions directly pertinent to surgery have been made by nonsurgeons.

This editorial was not written to decry the importance of surgical research that involves attempts to develop and utilize basic knowledge for the benefit of the surgical patient. On the contrary, the thesis to be set forth is that talented youngsters with scientific interests must have continuing opportunities not only for passive education but also for creative endeavors. Unless initiative is encouraged during the long years of medical school, internship, and surgical residency, the habit of creative thought and action will be lost. Such remarks are generally true of all the clinical specialties, but particularly of surgery.

One possible reason for the lack of creativity among surgeons is the environment provided by surgical training, which may be unfavorable for creative endeavor because of the need to develop clinical skills and to master technical procedures. This fact may even tend to discourage the selection of applicants with creative interests.

The restrictions encountered during the years of surgical residency make the pursuit of investigative problems almost impossible. For example, only half a year has been set aside for the resident to participate in investigative work, and much of that same half year should be devoted to such ancillary disciplines as physiology, pathology, and microbiology.

Most senior surgical residents are impatient to complete their training, so as to become financially independent, to attain mature stature in the community, and to achieve the level of technical competence necessary to obtain certification in their specialty. Postresidency years are not likely to be spent in the research laboratory unless appointments are appropriate and salaries are adequate.

Senior surgeons responsible for training programs may, by their actions, stress the importance of mastering intricate surgical procedures, thus inviting surgeons in training to accept technical proficiency as an ultimate goal. Worse yet, many good ideas have probably died a-borning because of an immediate cynical expression of disbelief by a mentor or a respected senior anxious to provide an overwhelming logical résumé of pertinent orthodoxy.

Under these circumstances, successful completion of surgical training is far less likely to result from outstanding demonstrations of creative thought than from an ability to cope with an endless series of practical crises in the operating room, on the ward, and in the outpatient department. Unfortunately, practicalities always demand first attention, and many a fresh idea is lost for no reason other than a lack of time to implement it.

Physiologists and psychologists have indicated that there is a strong correlation between age and creativity. Lehman has listed important achievements in various fields according to the ages of the persons involved. The peak of productivity for such achievements in the field of medicine was between the ages of 35 and 39 years.

It is interesting to note that the peak of creativity is later in the field of medicine than in the basic sciences. For example, the peak of creativity for chemists was reported by Lehman to occur between the ages of 28 and 32 years. As a matter of fact, it has

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been suggested that an individual who has failed to make an important contribution in chemistry by his mid-thirties rarely has been productive in that field. Likewise, the peak of activity for physicists, mathematicians, and many other scientists is generally reached before the age of 30. Great creativity in the arts occurs even earlier. Examples of major accomplishments by young artists, writers, and musicians are well known to everyone.

Friend and Zubek tested a large number of people in various occupations as to their abilities in critical thinking. These investigators concluded that the ability to think critically develops rapidly in the teens, reaches a peak during the twenties, and then gradually declines after the age of 40. Much the same age patterns were found among the subjects as to their abilities to detect implicit assumptions, to draw conclusions, and to evaluate arguments.

The findings of these and other psychologists cannot be ignored. Despite the popular conception of a successful scientist as a distinguished elderly man, his most important contributions to science were probably achieved before he reached the age of 25. Instances of creative work done in the later years of life are often cited in rebuttal, but almost all the persons involved were creative when they were young, and merely continued to be productive. *For maximum creativity, the habit of imaginative thinking should thus be established as early as possible.*

Roswell Park Memorial Institute has established a summer program for the purpose of giving young people the opportunity to work on research problems of their own in order to encourage more of them to choose careers in the fields of scientific research. Each summer, both clinical and nonclinical fellowships are open to high school, college, medical, and graduate students with demonstrated academic ability, and to a limited number of high school teachers. The candid, imaginative, probing remarks of the high school students on every subject are fascinating. The mature scientist can only view with awe and envy the ability of these young students to master laboratory procedures and to handle concepts which he has adopted only after long hesitation.

It would not be easy for an ordinary surgical resident to design and carry out procedures for isolating the nucleic acids associated with genetic transformation. This year, such a project had been independently undertaken by two summer program candidates who were *high school students*. One had already prepared beautiful fibrous desoxyribonucleic acid from tonsillar tissue obtained from her small town hospital! This kind of enthusiasm should not be stifled by the burden of 6 to 10 years totally devoted to receptive studies.

Much has been published about the wasteful content of various curricula. It would seem wise to review our educational programs for the medical sciences, to see if we cannot make better use of the most creative years. Perhaps technical competence in surgery and related fields of medicine could be achieved much earlier in life than it is at present. This would allow parallel growth in clinical judgment, teaching skills, and investigative work.

It must be admitted, of course, that only a few surgeons receiving earlier training would be highly creative. Nevertheless, such a program would enable the relatively uncreative surgeon to begin his career with a much greater understanding of scientific developments and their true significance, and would permit the fully creative surgeon to do far more.

The psychologic atmosphere of at least the first years of surgical training should be truly academic in nature. The last years will always be increasingly devoted to practical thoughts concerned with making a living and supporting a family—surgeons are amazingly creative in this particular sphere. The middle years, however, should be planned so that the surgeon in training can spend as much time as possible in investigative work. It hardly needs to be

emphasized that a favorable milieu for creative thought in the medical sciences must include facilities for both clinical and experimental research, with adequate opportunities for individuals to initiate new projects.

Efforts to salvage productive years from the long period of professional training are already being made. For example, the Johns Hopkins Medical School (2) is now putting into effect a revised program which will enable the well qualified medical student to dispense with 1 or 2 years of formal courses, and special provision is made to permit investigative work during the time saved. It will be interesting to observe the results of this particular experiment in medical education and to see how many other medical schools will eventually follow suit.

No less than any field of medicine, surgery requires creative studies in order to increase its therapeutic effectiveness. That being the case, it would seem desirable to reconsider the training program of young potential surgeons whose interests and talents warrant special attention.

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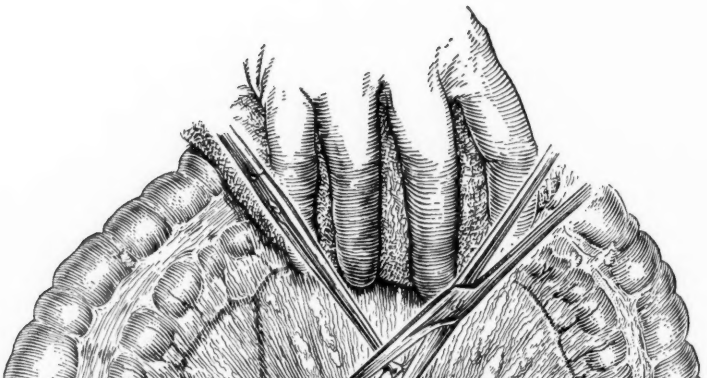

FIG. 1.

A Method of Handling the Jejunal Loop in Gastrectomy with a Posterior Anastomosis.—J. Englebert Dunphy.

THE SURGEON AT WORK

A METHOD OF HANDLING THE JEJUNAL LOOP IN GASTRECTOMY WITH A POSTERIOR ANASTOMOSIS

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IN THE CONVENTIONAL PERFORMANCE of a subtotal gastrectomy with posterior gastrojejunostomy, the stomach is pulled through an opening in the mesocolon and sutured in this position so that the anastomosis lies beneath and behind the mesocolon and colon. There are several disadvantages to this method: (1) There may be too great a drag on the stomach with a "slipping of the pants" and subsequent postoperative obstruction. (2) In very high gastrectomy, the transverse colon is pulled out of its normal position into the left upper quadrant and frequently it is necessary to make the hole in the mesocolon very close to the bowel. Both of these maneuvers favor the development of a gastrojejunocolic fistula should a marginal ulcer develop. (3) There is, of necessity, a double loop of jejunum entering and leaving the stomach in the free peritoneal cavity behind which herniation or a volvulus may occur. (4) Finally, the anastomosis is left in an inaccessible position should reoperation be necessary because of a postoperative complication.

Anterior anastomosis avoids most of these difficulties but it increases the likelihood of herniation behind the anastomosis and, in addition, it generally requires a longer jejunal loop.

The method of handling the jejunal loop described herein avoids all of these hazards because: (1) The afferent loop can be very short without causing the slightest tension. (2) There can be no "slipping of the pants" because the colon rests in its normal position, and the efferent jejunal loop can be made any desired length so as to avoid tension. (3) Posterior herniation behind the anastomosis is impossible. (4) The anastomosis is readily available in the event of postoperative obstruction or bleeding.

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TECHNIQUE

The essential steps of the technique are illustrated in Figures 1 through 8. Whether the anastomosis is done shortly after dividing the stomach proximally or after the completion of the gastrectomy is a decision which rests upon individual circumstances. At whatever point in the operation it is elected to perform the anastomosis, the steps of the procedure are as follows:

As shown in Figure 1, the mesocolon is opened by beginning the dissection at the ligament of Treitz. This is opened to the right in order to mobilize the fourth portion of the duodenum. The only structures which require consideration are the inferior mesenteric vein and the superior mesenteric artery and vein. Ordinarily, very adequate mobilization of the bowel can be obtained without disturbing or freeing these vessels.

The ligament of Treitz has been freed and the opening in the mesocolon enlarged as illustrated in Figure 2. This opening must be wide enough to permit the jejunum and its mesentery to pass through it without constriction.

Figure 3 illustrates the procedure as seen from above. The objective is to create an adequate opening in the mesocolon at its farthest point from the colon. This, in effect, brings the dissection directly across the body of the pancreas.

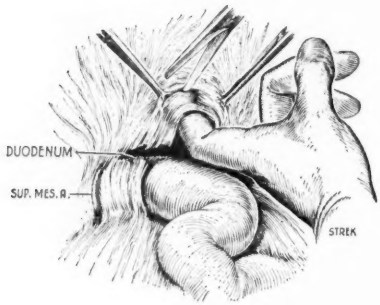

FIG. 2.

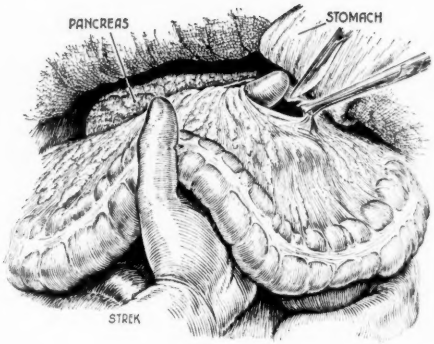

FIG. 3.

FIG. 4.

FIG. 5.

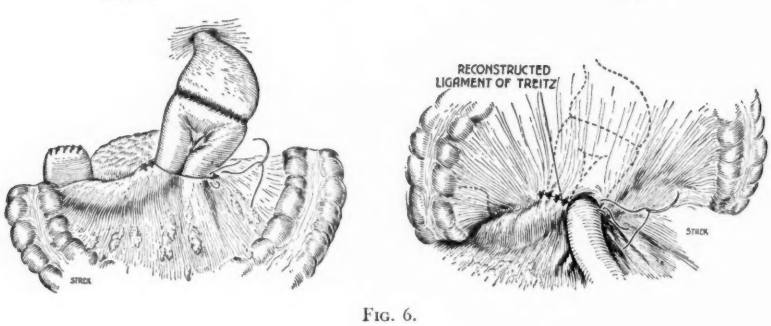

FIG. 6.

In Figure 4, the double loop of the fourth portion of duodenum and jejunum is drawn through the rent in the mesocolon. Because the ligament of Treitz has been freed, the fourth portion of the duodenum can be passed directly upward into the lesser sac.

The anastomosis may be performed in any of the conventional ways. Figure 5 shows the afferent loop being passed directly to the lesser curvature. At times the bowel may rotate so that it is technically easier to place the efferent loop at the lesser curvature. In my experience, it

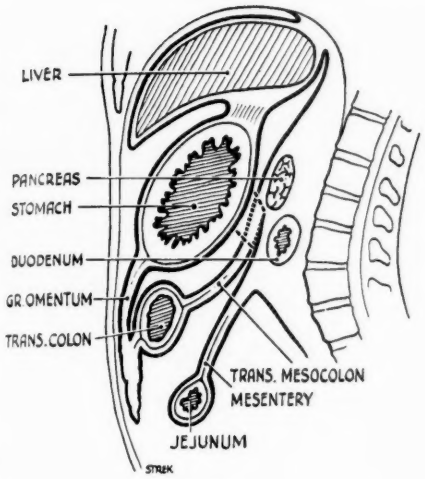

FIG. 7.

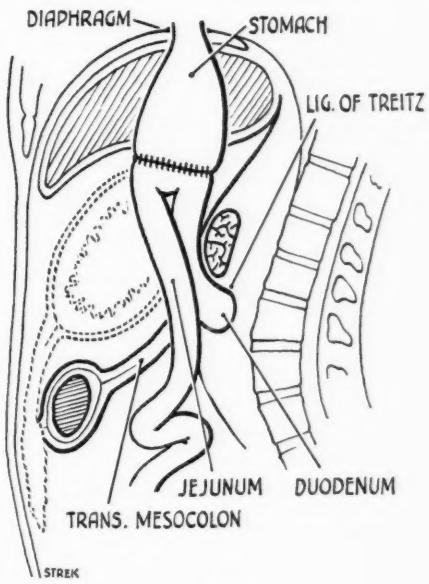

FIG. 8.

makes no difference whether the anastomosis is antiperistaltic or isoperistaltic.

The completed anastomosis is shown in Figure 6, left. The afferent loop lies completely in the lesser sac. The efferent loop and its mesentery pass through the rent in the mesocolon. This must be carefully closed by sutures which include the serosa of the efferent loop. Care must be taken in this step to assure fixation of the jejunal loop without constriction. A few of these sutures must include the peritoneal surface of the mesentery in order to completely close the opening.

Diagrammatically depicted in Figure 6, right, is the reconstructed ligament of Treitz. As one lifts the transverse colon, only a single loop enters the peritoneal cavity. The afferent loop lies above the mesocolon and is in what formerly was the lesser sac. This loop is exposed anteriorly, of course, because the gastrocolic ligament has been divided. If the omentum has not been removed, it can be rearranged over the loop if desired. In any event, there is easy access to the anastomosis in the event of early or late postoperative complications.

Preoperative relationships are depicted in cross section in Figure 7 showing the normal position of colon, duodenum, and jejunum. The duodenum lies posteriorly.

Postoperative relationships of the afferent and efferent jejunal loops, as well as the fourth portion of the duodenum, are shown in Figure 8. The efferent loop passes through the mesocolon at the location of the ligament of Treitz. The jejunal loops and the fourth portion of the duodenum lie behind the mesocolon.

My attention was first drawn to this procedure when performing a total gastrectomy with a posterior esophagojejunal anastomosis. In this instance, there is no stomach to pull through the rent in the mesocolon. The knack of opening the mesocolon directly at the ligament of Treitz so as to direct the afferent loop upward without angulation has the added advantage, of course, that only one loop passes through the mesocolon, and herniation behind the anastomosis is no longer possible.

No originality is claimed for this technique. It is an obvious step which probably has been used by many surgeons. Extensive experience with this method has convinced me of its usefulness. Since it has not been illustrated in the standard texts of operative procedures, it seemed desirable to describe it.

LOCAL COMPLICATIONS IN 167 PATIENTS WITH INDWELLING VENOUS CATHETERS

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PLASTIC INDWELLING VENOUS CATHETERS have come into increasingly common use since their introduction in 1945. They are often used to avoid multiple punctures during long term management. Also, catheterization by direct exposure of the vein—a "cutdown"—is often employed when superficial veins are not available in emergencies. Indwelling catheters are also used to assure a reliable route for rapid transfusion, with the intent of their early removal. As with any procedure, there are complications.

In an attempt to understand the causes for these complications, a review was made of the charts of patients who had mitral valvotomies which routinely involve bilateral saphenous catheterization before operation. The advantages of this selection include the following: (1) The cutdowns were all done in the same location with the same type of equipment. (2) The cutdowns were done under the same conditions by operators of similar experience (surgical interns and junior assistant residents). (3) The cutdowns were done by over 50 different individuals so that the results are representative of the procedure rather than the operator. (4) The patients were carefully followed because of the special interest of this surgical service in these cases. (5) The patients were followed not only by the surgical staff but also by a cardiac team who took particular interest in the appearance of the patients' legs and ankles.

METHOD

All 234 cutdowns included in this analysis were done in the surgical ward in the early morning before preoperative medication was given. The 2 legs were done simultaneously by 2 different operators with 2 completely separate sets of equipment. The technique including the routine use of masks, gloves, and sterile drapes is described and is similar to that of Kirkham.

The skin just proximal to the internal malleolus was infiltrated with 1 per cent procaine. A transverse incision was made over the saphenous vein which was then isolated by blunt dissection, carefully stripped of areolar tissue, and ligated distally with a medium black silk. A No. 18 or 16 polyethylene catheter was then introduced proximally for 3 to 6 inches, and a ligature of medium black silk was placed on the vein to hold the catheter. The skin was then closed with 3 or 4 vertical mattress sutures, one of which was often cut with long ends which were then tied around the emerging catheter.

When the valvotomy was completed, 1 catheter was usually removed either in the operating room or on the patient's arrival in the recovery room. The other catheter was routinely kept open overnight and removed the next day. In some cases, it was believed advisable to keep 1 or both catheters in place for longer periods, but in only 1 instance was this for longer than 3 days (Table II). The skin sutures were removed from 7 to 10 days after insertion.

In all cases, the patients received broad spectrum antibiotics throughout the period that the catheters were in place.

RESULTS

Three hundred charts were reviewed. Of the 600 cutdowns available, only 234 were considered suitable for study. The remainder were discarded for the following reasons: (1) The cutdowns were not done in the same manner in the earlier cases. (2) There was inadequate evidence for the length of time the cutdown was in place. (3) Anticoagulants were used in the immediate postoperative period for reasons not related to the cutdowns. (4) There was embolization to the leg. (5) There was lack of frequent descriptions of the ankle and leg for at least 2 weeks postoperatively.

Complications clearly attributable to catheterization. Of the 234 cutdowns selected for analysis, 26 produced a single local complication and 4 were responsible for 2 complications. The total num-

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ber of complications was 34. These included: (1) local pain without inflammation (11 cases); (2) massive local swelling (1 case); (3) infection of the cutdown site (10 cases); (4) separation of the wound after removal of sutures (2 cases); (5) phlebitis (10 cases).

The sites of 11 cutdowns were sufficiently tender so that the fact was reported in the chart together with the notation that other signs of inflammation were either minimal or absent. It is possible that this says less of the procedure than it does of the individual patient's response, particularly since 6 of the 11 occurred in 3 patients, i.e. bilaterally.

In 1 case a massive swelling developed at the ankle, and this was believed attributable to a leak about a catheter insecurely tied in place.

There were 5 instances of markedly inflamed wounds without suppuration and 5 cases in which incision and drainage were necessary to permit healing.

Of the 5 nonsuppurative wound infections, 4 occurred in 2 patients. Since the cutdowns were done simultaneously by 2 operators using 2 sets of equipment, the presence of infection, like the presence of pain without infection, may represent variation in the individual patients. In each of these 5 cases, the infection cleared rapidly with hot applications.

Of the 5 abscesses, 3 were noted to contain an unattached silk ligature, which was removed with the purulent contents. All 5 healed uneventfully by second intention.

Two wound separations were closed with adhesive tape without subsequent infection.

There were 10 cases of phlebitis, an incidence of approximately 4 per cent. Of the 10, seven were characterized by inflammatory signs along the course of the greater saphenous vein in the calf. In 4 of these, the phlebitis ascended as high as midthigh. In the other 3 cases, there was not only saphenous phlebitis but also inflammation of deep calf veins. All 10 cases of phlebitis cleared within 10 days when treated with bedrest, elevation, continuous local heat, and anticoagulants in 6 cases.

Of interest is the time of onset of phlebitis (Table I). As in the case of wound infection, the phlebitis appeared some time after removal of the catheters, in 1 case as long as 18 days later.

Of even greater interest is the fact of increased incidence of phlebitis in those cases in which the catheter was permitted to remain in place for longer periods of time (Table II). Whereas less than 1 per cent of the catheters removed within 12 hours were complicated by phlebitis, those left in 12 to 36 hours caused phlebitis in approximately 3 per cent of cases, and those left in over 36 hours produced phlebitis in approximately 38 per cent of the cases.

TABLE I.—POSTOPERATIVE DAY OF EMERGENCE OF INFLAMMATION

Type	*Postoperative day*
Ascending phlebitis	1, 2, 3, 5, 6, 6, 9, 13, 14, 18
Local inflammation	5, 9, 9, 9, 9
Wound abscess	8, 10, 12, 20, 40

TABLE II.—RELATION OF PHLEBITIS TO DURATION OF CUTDOWN

Hrs. cutdown was in place	*No. of cutdowns*	*No. of cases of phlebitis*	*Per cent phlebitis*
Less than 12	113	1	0.9
12 to 36	102	3	2.9
12 to 72*	120*	8†	6.7
36 to 72	8	3	37.5
Over 72	1	1	100
Total	234*	10†	4.3

*Includes 10 cases not in (12 to 36 hrs.) or (36 to 72 hrs.) because of uncertainty as to time of removal.
†Includes 2 cases not in (12 to 36 hrs.) or (36 to 72 hrs.) because of uncertainty as to time of removal.

Complications doubtfully attributable to catheterization. In the 300 valvotomies reviewed, there were 16 deaths within the first 30 days. In 3 of these a clinical diagnosis of pulmonary infarction had been made shortly before death, 2 being confirmed at autopsy. In none of these cases, however, were signs of phlebitis observed in the lower extremities. There were a number of cases of nonfatal pulmonary embolization but because of the frequent fever and various lung changes after valvotomy, the incidence of embolization could not be assessed.

In the 300 valvotomies, there was a single case of postoperative subacute bacterial endocarditis, occurring 6 weeks after removal of the catheters.

DISCUSSION

The reported complications arising from the use of indwelling venous catheters range from minor problems such as pain from mechanical irritation to such catastrophies as embolization of the catheter into the general circulation. The principal complication, however, is thrombophlebitis.

Some of the variation in incidence of complications is attributable to the use of different locations for the catheterization. However, even if we restrict our attention to ankle catheteriza-

tion we find a wide variation in the incidence of phlebitis: in this series approximately 4 per cent as compared, for example, with nearly 10 per cent in the series of Alexander and associates. These authors state: "If the tubing were automatically removed before 24 hours, phlebitis would be nonexistent." The significance of the length of time the catheter is in place is borne out by the present series (Table II). Similar conclusions were reached by Anderson who calculated on the basis of 153 cases that the chances are even (i.e. 50 per cent) that a catheter will produce phlebitis in 3⅓ days.

The longer the catheter is left in place, the more likely is the development of phlebitis. The possible causes include irritation by the catheter as well as by the infused solutions (hypertonicity, *p*H.); and for this reason many advise inserting a long length of catheter so the tip will lie freely within a larger vein and the solutions will be diluted. It is possible that there would have been a lesser incidence of phlebitis in this series if the catheter had been inserted more than 3 to 6 inches. However, the most likely cause of phlebitis is probably not mechanical or chemical, but bacterial. That this is so is suggested by the delay in development of the phlebitis, which usually occurred some days after the catheters had been removed (Table II). A relevant case is that of a patient who had bilateral wound inflammation. On the ninth postoperative day there was inflammation of both cutdown sites. On the thirteenth day, there was phlebitis extending upward from the cutdown site in 1 leg; and on the fourteenth day, in the other.

Probably the most convincing evidence that most catheter phlebitis is bacterial in origin is that cultures of indwelling catheters are so frequently positive. Indeed, Erwin reported Staphylococcus aureus upon culture from all catheters producing inflammation, and only rarely from catheters which did not.

SUMMARY

1. None of a series of approximately 600 greater saphenous cutdowns at the ankle was believed contributory to death.

2. In 234 cutdowns carefully followed for 2 weeks there were 34 complications, including 10 cases of minor wound infection and 10 cases of phlebitis. All of these responded rapidly to treatment including anticoagulants in 6 cases.

3. The incidence of phlebitis rises rapidly the longer the catheter remains in place.

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MARSHALL-MARCHETTI OPERATION FOR PROLAPSE OF VESICAL NECK

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IT SEEMS PARADOXIC that an operation originated to correct urinary incontinence could also be adapted to relieve urinary obstruction. However, the application of the Marshall-Marchetti operation to correct prolapse of the vesical neck is the subject of this report. Perusal of the urologic literature has failed to reveal a similar case, but other instances of this apparently rare condition may have been observed.

CASE REPORT

A 44 year old white woman consulted one of us (G.F.M.) in June 1957, complaining of difficulty in expressing urine after the birth of her first child, 21 years before. This symptom became more distressing during the years and she had become incapacitated in the year prior to consultation. During this period of time, the urinary stream became so small that the patient required 15 to 30 minutes "to empty her bladder." There were no other complaints which were referable to the urinary tract.

The patient's first 2 pregnancies terminated in vaginal delivery. The first, according to the patient, was accomplished by a difficult forceps operation. The infants weighed 8 pounds, 8 ounces (3,856 gm.) and 10 pounds (4,536 gm.), respectively. A third pregnancy was terminated by classic cesarean section in 1946 because of central placenta praevia, and a fourth by cesarean section in 1947. Cesarean supravaginal hysterectomy had been performed in 1949 because of a defective uterine scar.

The patient was an intelligent, co-operative, obese woman, 5 feet 2 inches tall, weighing 225 pounds. General physical examination revealed nothing abnormal other than the obesity. Pelvic examination showed adequate vaginal supports, without evidence of cystourethrocele or rectocele. The cervical stump was clean, mobile, and well suspended. Palpation of the adnexa and cul-de-sac yielded normal findings, as did digital examination of the rectum.

Microscopic examination of vaginal secretion indicated normal estrogen effect and absence of abnormal cells. Tests of urine for protein, sugar, erythrocytes, leucocytes, and bacteria were negative. Intravenous urograms showed normal kidneys and ureters.

Cystoscopy showed a normal posterior vesical lip. Upon rotating the instrument it was observed that the anterior vesical neck hung down as a fold over the upper half of the vesical orifice (Fig. 1). There was moderate hypertrophy of the trigone but no trabeculation of the detrusor. There was no residual urine; the capacity of the bladder was 360 milliliters. Urethroscopy showed the prolapse of the vesical neck as described. The urethra was normal. Cystourethrography likewise revealed prolapse of the anterior aspect of the vesical neck (Fig. 2).

With the patient under general anesthesia the retropubic space was exposed through a low midline abdominal incision. The site of prolapse was identified, and 6 sutures of No. 0 chromic catgut were placed in crescentic arrangement (Fig. 3a) into the redundant area. These were suspended to the rectus fascia. Sutures were not placed into the wall of the urethra since the urethra was not involved in the prolapse, nor was it necessary to anchor the sutures into the periosteum of the pubis; the proximity of the rectus fascia rendered this structure more suitable. The vesical neck was defined by the bag of a 30 milliliter No. 24 French Foley catheter (distended to 15 ml.) within the bladder.

In our experience, the low lithotomy position has been helpful in placing the suspension sutures in the Marshall-Marchetti procedure. This position permits simultaneous access to the vagina and retropubic area in pelvic operations. It is attained by placing the patient in the dorsal decubitus position with knees spread apart, supported by low, well padded leg rests. Legs are wrapped in elastic stockings.

Using an angulated needle holder, the surgeon places the sutures with his right hand. At the same time, he exerts upward pressure on the vesical neck with the fingers of his left hand, through the vagina (Fig. 3b). This maneuver brings the vesical neck into the operative field and steadies it while the sutures are being taken. More precision is lent if the surgeon, rather than an assistant, holds up the neck. Bimanual palpation is of aid in judging the position of the sutures and the depth to which they are laid. The objective is to take a firm bite in the muscularis of the bladder (or urethra) without penetrating the mucosa.

After the operation was carried out according to the described procedure, the Foley catheter was left in place for 8 days. After removal of the catheter, the patient was able to void without difficulty, and the stream of urine was expressed with adequate force. Cystourethroscopy showed a normal urethrovesical outlet. At examination 18 months after operation, the patient was in normal health.

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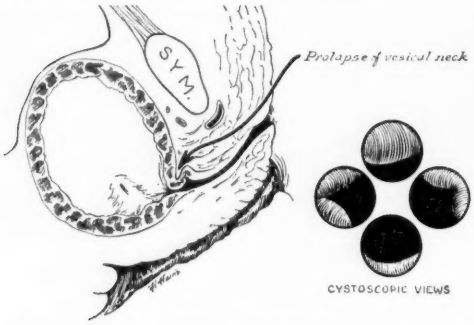


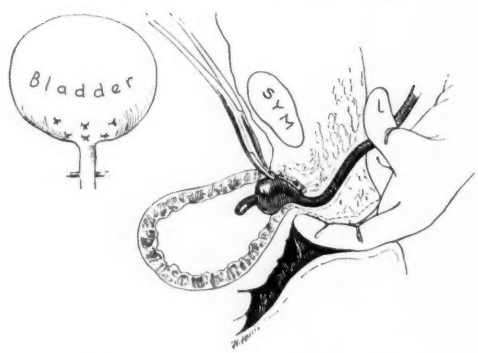
FIG. 1. Diagram and cystoscopic views of prolapsed vesical neck.

FIG. 2. Cystourethrogram showing prolapse of anterior aspect of vesical neck.

DISCUSSION

Prolapse of the vesical neck is apparently an infrequent cause of obstruction to the lower urinary tract. In the case reported, the onset of the patient's symptoms shortly after her first parturition suggests the possibility that the initial forceps delivery caused the responsible trauma. This may have been aggravated by the vaginal delivery of a second large child 2 years later; obesity may have been another contributing factor. The absence of cystourethrocele is indication that the vesicovaginal fascial plane was not the site of injury, and since the patient did not experience any urinary stress incontinence it seems that the normal posterior relationships of the vesicourethral junction were not disturbed.

The anatomic defect which led to the prolapse seemed to be rupture of the medial pubovesical ligaments. Anatomically, the bladder is supported from below by the levator ani muscles and the urogenital diaphragm; above, it is suspended by the medial and lateral pubovesical ligaments. Similar to the supporting structures of the uterus, these ligaments arise from condensations of endopelvic fascia. They correspond to the puboprostatic ligaments in the male. The site of prolapse of the vesical neck, as indicated by the arrow in Figure 1, is the point of origin of the medial pubovesical ligaments which insert into the bodies of the pubes. Rupture of these structures could permit relaxation and eventual prolapse of the vesical neck. Retropubic suspension restored the normal relationship provided by medial pubovesical ligaments. It is unlikely that classical cesarean section and/or cesarean supravaginal hysterectomy damaged pubovesical ligamentous supports.



a b

FIG. 3. a, Arrangement of suspension sutures to correct prolapse of vesical neck. b, Low lithotomy position facilitates placing sutures by simultaneous access to vagina and retropubic region.

SUMMARY

Prolapse of the vesical neck, in a 44 year old multipara, was relieved by the Marshall-Marchetti operation. This unusual obstruction to the lower urinary tract was apparently caused by rupture of the medial pubovesical ligaments during parturition. The value of the low lithotomy position in placing suspension sutures in the vesical neck is described.

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DIAGNOSTIC CONSIDERATIONS IN FRACTURES OF THE CARPAL SCAPHOID BONE

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THE PROBLEMS concerning the diagnosis of the fractures of the scaphoid bone of the hand have been the subject of several reports in recent years. Although there has been widespread interest in the problem, no satisfactory progress has as yet been noted. The same difficulties which have hampered other investigators in the field are still being encountered today.

The importance of the problem is well known to those dealing with it. The period of unfitness of the patient for work is considerable and may extend, at times, for more than a year. The prognostic uncertainty which is always present in these cases is also cause for concern.

During treatment, changes in the bone structure which are not easily interpreted may develop. There have been known instances in which the fracture line has disappeared in the course of treatment but an irregular sclerotic pattern has persisted. The picture is not compatible with nonunion, nor can it be accepted as a healed fracture. The difficulties in determining whether to continue immobilization to the point of homogenization or to remove the plaster cast and continue active physiotherapy are apparent.

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However, not every case constitutes such a problem; otherwise, the treatment of fractures of the scaphoid bone would be much more complicated. Fracture and healing, diagnosis and treatment, usually take an uneventful course, and only the relatively prolonged healing time disturbs both the patient and surgeon.

Several problems were encountered while studying this condition, for which no solution could be found and prompted us to search for new means of obtaining an accurate diagnosis.

METHOD

Generally, when the line of fracture is parallel to the direction of the roentgen rays, detection of the fracture in the usual positions is easy (Fig. 1).

Our experience shows that in addition to the common fractures there are also several variations in which the line of fracture does not lie in a vertical position to the roentgen rays, but in a lateral or diagonal position. In such instances, the 2 fragments of the fractured bone cover one another and the fracture line is therefore not visible (Fig. 2).

The presence of such fractures can be established with certainty only when the roent-

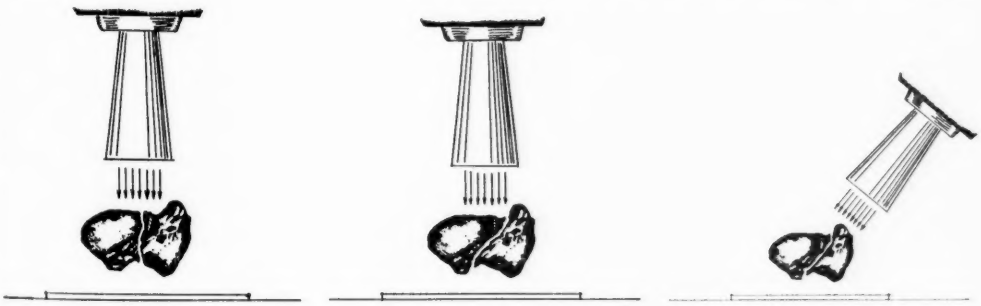


FIG. 1. a FIG. 2. b

FIG. 1. The fracture line is parallel to the direction of the roentgen rays.
FIG. 2. The fracture line is in a diagonal position. The two fragments cover one another. a and b, Positions for "searching" with roentgen rays.

FIG. 3.

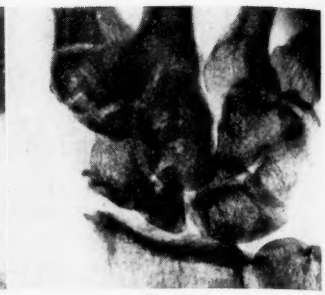


FIG. 4.

FIG. 5.

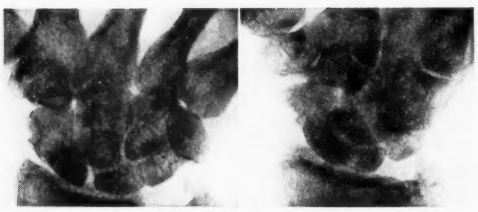


FIG. 6.

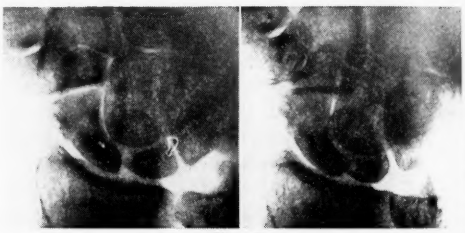


FIG. 7.

FIG. 8.

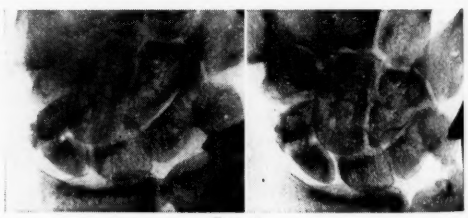


FIG. 9.

FIG. 3. Case 1. The structure of the scaphoid bone showed indistinct changes. Arthrotic changes of the wrist joint are visible in the area between the scaphoid bone and the radial styloid process.

FIG. 4. Case 1. Roentgenograms showing nonunion of a fracture of the scaphoid bone taken with the tube at a 30 degree distal projection.

FIG. 5. Case 2. Roentgenograms taken in usual way showing scaphoid fracture with distinct separation.

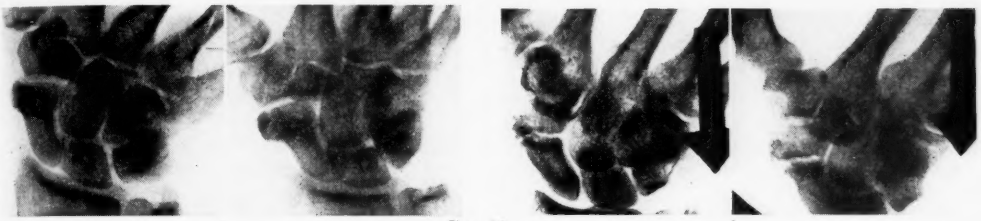
FIG. 6. Case 2. Two months later the distance between the fragments decreased and the fracture line is no longer distinct.

FIG. 7. Case 2. After 4 months the fracture line is no longer recognizable. Only a slight irregularity persisted.

FIG. 8. Case 2. No progress noted 1 month after roentgenogram shown in Figure 7.

FIG. 9. Case 2. A distal projection of 35 degrees revealed nonunion of the scaphoid bone fracture.

FIG. 10.



a FIG. 11. b

FIG. 10. Case 3. Nonunion of the fracture of the carpal scaphoid bone disclosed by roentgenograms taken from external distal projection, 20 to 30 degrees.

FIG. 11. Case 4. a, Roentgenograms taken in usual way. b, Nonunion revealed by roentgenogram taken at proximal projection.

gen rays are correctly directed, i.e., parallel to the line of fracture. In order to visualize the fracture clearly, the positions for the x-ray examination should be altered accordingly. Following this conclusion, we have adopted a roentgenologic technique which differs from the accepted in determining fractures of the scaphoid bone. In every case in which suspicion of a lesion of this bone is clinically manifest, and in which the usual positions show a structural change, the patient undergoes a thorough examination and the tube is set at different positions for "searching," i.e., projections in the direction of the possible fracture line (Fig. 2).

Better distinction between the parts of the fractured bone has been made possible in many cases by various projections.

CASE HISTORIES

CASE 1. Z. H., a 41 year old man, was seen after a fall during work. He complained of great pain in the left wrist. Upon examination, slight swelling, pain on pressure, and distinct limitation of movement were observed. The usual x-ray examination showed arthrotic changes of the joint, mainly in the part between the scaphoid bone and the radial styloid process. The structure of the middle of the scaphoid bone showed indistinct changes. Figure 3 shows a probable cleft of the bone.

The case involved arthrotic change of long standing. The differential diagnosis implied the possibilities of a nontraumatic arthrosis, an arthrosis after the healing of a broken scaphoid bone with a new fracture, and an arthrosis with nonunion which showed overlapping of the fragments in the usual positions of examination. The use of different projections in supplementary examinations led to a solution. Roentgenograms taken with the tube projected distally to a 30 degree angle enabled us to see the separated fragments of the fracture and nonunion of an old fracture, the probable origin of the arthrotic changes (Fig. 4).

CASE 2. D. I., a 23 year old man, was examined on September 8, 1957 after he had fallen on his hand. The examination showed a swelling of the joint, a filling of the anatomic snuff-box, and hypersensitivity to pressure. The usual x-ray examination did not show any changes. A plaster cast was applied and the examination repeated after 10 days, but again no changes were seen. The plaster cast was then removed, and the patient returned to work. Five months later on February 13, 1958, there was a second injury of the left hand. The clinical symptoms were similar to those of the first injury. The usual x-ray examination revealed a fracture of the scaphoid bone with a distinct distance between the parts (Fig. 5).

The hand was put into a plaster cast for 2 months,

and the x-ray examination made after its removal showed complete healing (Fig. 6). The distance between the fragments had decreased and union had begun to develop. The fracture line was no longer distinct. A control examination performed 1 month later, showed union of the parts with an indistinct fracture line. Four months later, on June 15, 1958, the plaster cast was removed for the third time, and the fracture line was no longer recognizable. A slight irregularity still persisted at the spot. Because of this and also in order to obtain greater assurance of union, the hand was put in plaster for another month (Fig. 7). On July 15, 1958, a control examination showed no progress (Fig. 8), and doubt as to the true condition of the fracture began to arise.

In this case too, the state of the fracture was clarified by the use of various projections. A distal projection of 35 degrees revealed nonunion of the fractured scaphoid bone. (Fig. 9).

CASE 3. N. A., a 25 year old man, was sent to our department for clarification of the nature of a fracture. The trauma had occurred a year and a half previously, and the patient had been treated in one of the local hospitals. During treatment the fracture line disappeared, but certain changes in the bone structure persisted which caused immobilization for nearly a year. Upon assumption of healing, the plaster cast was finally removed. In our department, an examination performed with the use of an external distal projection, 20 to 30 degrees, disclosed nonunion (Fig. 10).

CASE 4. K. S., a 26 year old man, was examined by us 4 days after trauma had occurred. Examination revealed a slight swelling of the wrist, tenderness on pressure in the snuff-box area, and limitation in the flexion of the right hand. Fracture of the scaphoid bone was seen on the roentgenogram obtained from the physician in charge. Because of the shape of the fracture and certain changes in the bone pattern, the projection method was used. In proximal projection, nonunion was revealed. Later we obtained a detailed anamnesis from the patient wherein he stated that there had been pain in his hand for more than 6 months; at that time he had changed to a new job which necessitated rotating movements of the hand (Fig. 11).

SUMMARY

The problems arising in the diagnosis and treatment of the fractures of the carpal scaphoid bone are many. Our aim has been to establish only the principles of our approach toward the diagnosis of those fractures which cannot be obtained by the usual, accepted methods.

Projections of the tube at various angles make visualization of the fracture line possible. In cases in which fracture is doubtful every projection angle should be used in order to demonstrate this.

CLINICAL EXPERIENCE WITH SUPRAVITAL STAINING IN SURGERY OF THE PAROTID GLAND

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STAINING of the parotid gland has proved to be an aid in surgery of the parotid region. From the time of the development of this technique in the laboratory (1) in 1956, the procedure has been tried in the operating room 37 times. The conclusions that were drawn in an earlier preliminary report (2) are corroborated here in the analysis of a larger number of operations for more diversified pathologic conditions.

TECHNIQUE OF INJECTION

Immediately after endotracheal intubation for anesthesia, dilatation of the parotid duct orifice is accomplished by the use of nasolacrimal duct probes, sizes Nos. 00, 0, and 1. Polyethylene tubing No. 22 gauge is introduced 1 to 3 centimeters into the papillary opening and held in place by the use of a smooth thumb forceps or a small hemostat. A sterile 1 per cent aqueous solution of methylene blue is injected via a 5 cubic centimeter syringe attached to the tubing by a No. 22 gauge needle. This should be injected slowly and easily over a period of 20 to 30 seconds. Approximately 3 cubic centimeters will distend the gland moderately and this amount is usually enough to stain the gland adequately. On withdrawal of the tubing, a dry gauze 4 by 4 inch sponge, folded in two directions to make a thick square, is placed over the duct opening. The preparation of the skin and draping of towels can follow immediately. During this 5 minute period required for preparation of the operative field, the methylene blue is fixed by the gland and will no longer spill and stain adjacent tissues.

APPEARANCE OF STAINING AT OPERATION

After forward reflection of the skin and subcutaneous tissues the normal parotid gland appears definitely blue, dulled only slightly by the containing capsular fascia. Only when the dye fails to reach the gland because of blockage of the ductal system does the gland fail to stain. Sometimes a partial block produces only patchy blue staining in a mottled pattern. The part of the gland containing a pathologic condition, usually tumor or cyst, is not stained, in sharp contrast to the blue of the normal glandular structure. The facial nerve branches maintain their white color and can be readily differentiated from gland. Cross-cutting the blue gland does not spill and stain adjacent tissue. Numerous small tags of blue gland remaining after the tedious so called "total parotidectomy with facial nerve preservation" attest to the difficulty of en bloc type removal by this procedure. Some blue dye on the dressings immediately over inserted drains will be present for a day postoperatively but the methylene blue is readily absorbed by the blood stream. In the dosage of dye used, no persistent local edema has been noted. The urine may be green or blue for 24 hours if only a small resection has been performed, leaving in the greater percentage of the stained gland. The dosage is too small to produce any systemic symptoms or signs.

CLINICAL EXPERIENCE

With this technique, 37 operations have been performed. In only 2 patients has the staining procedure been impossible and in both because the duct was blocked near its orifice. In 1 patient there was a stricture due to scar from a through-and-through laceration; tumor blocked the duct of the other. Staining described as fair was obtained in 2 patients, one who had had chronic parotitis with repeated abscess formation requiring previous incision for drainage. The other patient had a persistent parotid fistula from a previous attempt at tumor removal, through which much of the dye leaked out on injection. In the 33 others, the staining was good. The pathologic entities for which surgery was performed in this series are listed as follows: mixed

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tumor in 19 cases; carcinoma in 6; papillary cystadenoma lymphomatosum in 3; chronic parotitis in 2; lymphoma in 2; sarcoma in 1; traumatic cyst in 2, calculus in duct in 1; and severed facial nerve in 1 case. The following procedures were performed for the various pathologic conditions found in the 37 patients: total parotidectomy (sometimes with neck dissection) in 11 cases; superficial lobectomy, 14; partial parotidectomy (removal of tumor with core of normal surrounding tissue), 11; repair of facial nerve trunk, 1 case.

Although a comparison of operating times for a similar series without the use of the staining method does not lend itself to statistical analysis, it is our impression that the surgery is facilitated.

CONCLUSIONS

Unless there is mechanical blockage of the ductal system, the gland stains well. The sharp color contrast aids in differentiating normal gland from pathologic conditions and facilitates the finding and dissection of the facial nerve twigs. Partial removal of tumor with a wide core of surrounding normal gland can be done faster and more accurately, and superficial lobectomy is technically easier. Total parotidectomy is simpler and more complete by the removal of all blue tissue.

SUMMARY

1. The technique of supravital staining of the parotid gland by methylene blue is set forth.

2. Findings at operation, after staining of the gland, are described.

3. It is concluded that this staining technique facilitates the operative procedure.

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The Book Shelf

RUDOLF HEIDENHAIN OF BRESLAU

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THE GASTRIC POUCH is a familiar tool to the gastrointestinal physiologist and the name Heidenhain is almost synonymous with the gastric pouch. It is interesting that although surgeons associate the name Heidenhain almost exclusively with gastric physiology, this is perhaps to nonsurgeons the least known of his many works. This phase of his research was not even mentioned in the extensive obituary which appeared in the *Berliner Klinische Wochenschrift* in October 1897.

Rudolf Heidenhain was born in Marienwerder, Germany, on January 29, 1834. His father was a Prussian physician and an amateur poet; his 5 brothers also became physicians, although none was as widely known as he. After an exceptional record as a young student in his home town, he studied medicine in Königsberg, Halle, and Berlin, where he was a student and associate of one of the great physiologists of the time, Du Bois-Reymond. As a thesis for his doctor's degree, he published a dissertation on the innervation of the heart.

After completing his medical studies, Heidenhain worked in the private laboratory of Du Bois-Reymond in Berlin on the physics of nerve and muscle function. During this period, he demonstrated that rapid mechanical stimulation of a nerve produced tetanic contraction of striated muscle.

Heidenhain's scientific interests were broad and in 1857, while at Halle, he published the results of his investigations of blood volume. In 1859, at the age of 25, he was appointed Professor of Physiology and Histology at the University of Breslau, which was an exceptional attainment, and remained at that institution until his death nearly 40 years later.

So voluminous were his publications in the next 10 years that many of them were published in book form as symposia from the Department of Physiology at Breslau. Included in these works were many improvements and extensions of the ideas of Helmholtz and Du Bois-Reymond on muscle metabolism.

Heidenhain's life work, however, dealt with the process of glandular secretion, from which came Heidenhain's law, which states that glandular secretion is an active process and associated with histologic changes in the structure of the gland. His studies on gastric secretion are an example of this. Heidenhain demonstrated that there were two main cell types in the gastric mucosa; these he called: (1) the chief or central cell, and (2) the parietal or border cell. In the fasting state, he found the chief cells to be large and clear, and during the first 6 hours after ingestion of food, both the chief and the parietal cells increased in size. Following this, the chief cells were observed to become gradually smaller for a time, then assume their fasting size.

Although not the first investigator to produce an isolated gastric pouch with external fistula, Heidenhain was one of the first to do so successfully. This work was published in 1878, but apparently was not pursued, because it remained for one of his pupils, Ivan Pavlov, to perfect and improve upon his technique. Pavlov reasoned

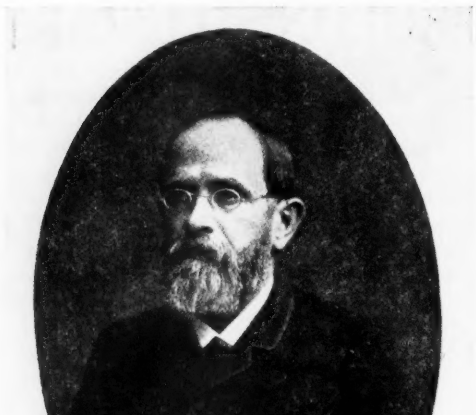

FIG. 1. Rudolf Heidenhain, 1834–1897. Professor of Physiology at the University of Breslau, 1859–1897. (Reproduced from *Arch. ges. Physiol.*, 1898, 72: 221.)

that the Heidenhain preparation was not totally successful because of damage to the vagus nerves during the procedure, and prepared an isolated gastric pouch with intact innervation. This later preparation is known to all of us as the Pavlov pouch, but in Pavlov's own laboratory, it was always referred to as the Heidenhain-Pavlov pouch. It is to be noted that Heidenhain's original pouch preparation was primarily pyloric in origin, rather than from the corpus of the stomach as at present. It is also to be noted that the original pouch was obtained by wedge resection interrupting the continuity of the stomach which was then restored by anastomosis. The modern pouch is obtained by removing the greater curvature portion of the corpus. Also of interest is Heidenhain's statement attributing his success, where Klemensiewicz had failed previously, to the utilization of "Lister's antiseptic method." A translation of the original epoch-making article follows (1):

The formation of pepsin in the pylorus glands is still being disputed despite numerous evidence, particularly by Ebstein and Grützner, who have worked together as well as separately on this problem. The reasons for this opposition more often than not appear to be based upon preference for the old, ingrained theories, rather than objective judgment of new and proven facts. One of the most excellent publications dealing with these problems is by Klemensiewicz in Rollet's Laboratory. This investigator had the bold idea to isolate the pyloric part of the stomach in a manner similar to Thiry's isolation of loops of the small intestine. Klemensiewicz separated the portio pylorica in dogs from the intestine and the fundus of the stomach by two transverse incisions, anastomosed the two by suture to create intestinal continuity, and then made an artificial blind pouch with the pylorus part which had a fistulous opening to the outside. Unfortunately, none of these dogs survived more than 72 hours postoperatively, the majority died even sooner. Nonetheless, this period of time was sufficient to obtain an alkaline secretion of tenacious, mucous nature, of course often mixed with blood and pus, which when mixed with 0.1 per cent hydrochloric acid was capable of dissolving fibrin in a short period of time, in fact as fast as the secretion of the fundus part of the stomach.

When Klemensiewicz concluded from these experiments that the pylorus glands without doubt participate in the formation of pepsin, his opponents advanced their last and rather improbable argument: The mucosa of the pylorus normally was covered with a very thick layer of mucus, in and upon which pepsin secreted by the fundus was retained. This mucus was only gradually secreted, the period of observation was too short for a complete cleansing of the surface of the artificial pylorus pouch; therefore, Klemensiewicz after all only had obtained pepsin of the fundus.

Attempts were made by Klemensiewicz to keep the dogs alive after creation of the pyloric fistula to invalidate the above argument. Where Klemensiewicz failed, I was successful in three out of six cases by using Lister's antiseptic method.

One of three dogs which survived the operation for a longer period of time has to be excluded, because the mucosa of the fundus had not been completely separated, which soon became apparent in the nature of the secretion. During digestion, the fistula excreted tenacious mucous material of strong alkaline reaction, and at the same time there was a thin, liquid acid secretion which did not mix with the mucous material; fibrin was dissolved rapidly by this secretion. This experience taught us to examine the edge of the mucosa microscopically after separation of the portio pylorica, so that all fundus glands were definitely excluded from the pyloric pouch before finishing the operation.

One of the remaining two dogs had to be sacrificed on the 14th postoperative day, because of a severe stricture at the junction of the stomach and intestine which did not permit the passage of food. This resulted in an enormous stomach enlargement; the animal began to vomit, ultimately could not retain water, lost weight and strength, and finally had to be released from its misery.

In the meantime, for 12 days the pyloric pouch excreted tenacious, diaphanous, alkaline mucus. One floc of this material mixed with 5 to 10 cubic centi-

meters of hydrochloric acid 0.1 per cent digested fibrin within 30 minutes to 1 hour.

Up to this point I am in agreement with Klemensiewicz; however, I have never been able to confirm his observation that the pyloric secretion contained diastatic ferment. All experiments failed to convert a starch solution into sugar with this secretion in an incubator at 40 degrees C.

After the animal had been sacrificed, microscopic examination of the mucosa of the pyloric pouch showed the complete absence of fundus glands.

The last dog upon which I wish to comment, was operated on July 5. The evening of July 7, it was given 2 tablespoons of milk for the first time and the same amount on the next day. On July 9, besides milk, it had small portions of ground meat. In the beginning, it is of great importance to keep the portions small to avoid vomiting.

The animal was observed daily until July 26, twenty-one days postoperatively, and was in good condition. Each time after feeding, slow secretion began which increased for 5 hours. The amount secreted was small, 2 to 3 cubic centimeters per hour. The secretion was constantly alkaline, tenacious, mucous, diaphanous, and rich in pepsin and rennet ferment. When mixed with 0.1 per cent hydrochloric acid it dissolved fibrin rapidly and caused complete coagulation in fresh milk without formation of acid in a warm place from 15 minutes to an hour; however, again no diastatic ferment was present.

After I returned from a trip in mid-September, the fistula had narrowed considerably but still secreted the pepsin-containing mucus.

The above observations, one of them over a period of 10 weeks, I feel should remove the last doubts regarding the formation of pepsin in the pylorus glands and should finally arbitrate the drawn-out dispute in which particularly Grützner was forced to participate for such a long time.

In addition to his work on gastric secretion, Heidenhain studied the secretion of the salivary glands, the pancreas, and the breast, and most of this material was published in 1880 in a 400 page essay in Hermann's *Handbuch der Physiologie*.

The observations on the secretions of the stomach and other glands were extended to form the basis of Heidenhain's theories on the formation of urine and lymph. Heidenhain stated, in opposition to Ludwig, that the formation of urine was independent of blood pressure and was not a process of simple filtration by the glomerulus, but rather an active process of secretion. He attributed the secretion of water to the glomerulus and the secretion of solids to the renal tubules.

Some of Heidenhain's last articles dealt with hypnotism, which he thought was an artificially produced cataleptic state produced by paralysis of the ganglion cells of the cerebral cortex. He also wrote an explanation of the necessity for animal experimentation and vivisection.

Rudolf Heidenhain died unexpectedly in 1897, shortly after his sixty-third birthday, of an intestinal ailment, said to have been a duodenal ulcer. It is of collateral interest that the death of Heidenhain, Professor of Physiology and Histology at Breslau, occurred in the same year, 1897, when Mikulicz, Professor of Surgery also at Breslau, wrote one of the earliest collective reviews on the subject of the surgical treatment of perforated peptic ulcer. We have no record that the one had a perforated ulcer or was a patient of the other, but at least the coincidence is of interest.[1] Heidenhain was considered by his biographers to have been at the apex of his career at the time of his death, and the world literature records the loss which was felt by the scientific world.

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[1]In Mikulicz's article published in 1897, he reported the first recorded simple closure of a perforated ulcer in 1880, with death of the patient within 3 hours, while the first successful application of simple closure was by Heusner in 1892, reported by Kriege. This successful operation, incidentally, was performed in the patient's home in Barmen, Germany.

Reviews of New Books

ONCE IN A WHILE a book appears which really "hits the spot." I believe the *Atlas of Roentgenographic Measurement*[1] is an example of such a book. The authors have gathered isolated tables and graphs into one small, 176 page volume to give us the known normal roentgenographic measurements. Obviously, some of these measurements have much wider acceptance than others. It is hoped, however, that with this presentation, greater use will be made of the available methods of measurements.

After a preliminary discussion of the geometric distortion of the roentgen image and its correction, the following various systems are presented: skeletal, respiratory, cardiovascular, gastrointestinal; the spleen and adrenals; the urinary tract and pelvimetry and fetometry. Line drawings, charts, and photographs are used to illustrate the points and methods.

—*R. B. Lewis.*

FEW PHYSICIANS AND SURGEONS limit their interests to the foot and the diseases or injuries that may disturb its function. DuVries' *Surgery of the Foot*[2] is based on the experience of 30 years in this specialty. One may be inclined to criticize the author for not stressing the conservative rather than the operative approach in many of the conditions discussed until he recalls the title of the text. DuVries mentions that many of the entities for which surgical treatment is outlined can be treated successfully by more conservative methods. A companion volume discussing these conservative methods would be welcome also.

This book is well illustrated, and those surgical procedures which the author has found to be of value —many of which were altered by him and are referred to as the DuVries modifications—are described in detail. Other well recognized procedures are not mentioned. No attempt was made to discuss in completeness the treatment of paralysis, talipes, and a number of other severe disabilities of the foot. The book is directed toward the commoner disabilities which develop, for the most part, because the foot is shod.

Outstanding are the chapters on disorders of the skin and on diseases and deformities of the toenails. Rational and oftentimes ingenious but simple surgical procedures for the treatment of corns, calluses, ingrown toenails, and other allied conditions are described. I cannot agree, however, with the premise that many of the surgical procedures which are outlined are suitable for performance in the office of the average, busy practitioner.

This text will be of especial value to the orthopedic surgeons and those general surgeons who at times are called upon to care for diseases and injuries of the foot.

—*Paul R. Lipscomb.*

VOLUME II of *Transplantation of Tissues*[3] is an encyclopedic report of experimental and clinical observations and experiences in the transplantation of skin, cornea, fat, nerves, teeth, blood vessels, endocrine glands, organs, peritoneum, and cancer cells. Volume I, published in 1955, was written by Lyndon Peer himself. In Volume II, he has written several chapters but has chosen contributors with special knowledge and experience in the transplantation of other tissues. These include among others: Sterling Bunnell on nerve transplantation, Ramon Castroveijo on corneal transplantation, Ralph Deterling on blood vessel transplants, E. J. Eichwald on cancer cells, Blair Rogers on the transplantation of skin, David Hume on organ transplants and, above all, P. B. Medawar, whose demonstration in 1944 of the phenomenon of accelerated rejection has been the stimulus for many of the exciting investigative problems on homotransplantation reported in these two volumes.

Medawar introduces his chapter with a discussion of wound healing and then proceeds to the possibilities of the use of homogenous transplants in the severe wound or the severely diseased tissue. He points out that in the experimental animal the presence of an epithelial sheet covering a granulating surface does not alter the progress of contraction which takes place in the wound itself as it matures. It is his thought that this contraction is probably a function of the fibroblasts. His experimental findings confirm the often made surgical observation that "the thinner a skin graft, the feebler is its power to hold contraction at bay." He emphasizes that "from the standpoint of final repair the advantages of providing precocious epithelial cover by tissue culture or other more expeditious means are quite illusory." He discusses the immunology of homotransplantation, modification of the homograft reaction, acquired tolerance and enhancement, to all of which he has contributed so much. Fortunately, he retains an optimistic point of view about future possibilities of penetrating the mysterious barrier.

The reviewer of Volume I commented on the extensive bibliography, which is even larger in several of the chapters in Volume II. He was critical of the lack of alphabetic order in these references which are recorded in the order in which they appear in the text. It happens that in both volumes there is an alphabetic "Index of Names" in the back of the book which serves essentially the same purpose.

It would be a monumental task to read this important volume from cover to cover. As a reference book for those interested in the history as well as the recent

[1]ATLAS OF ROENTGENOGRAPHIC MEASUREMENT. By Lee B. Lusted, M.D., and Theodore E. Keats, M.D. 176 pages, 119 illustrations. $9.00. Chicago: The Year Book Publishers, Inc., 1959.

[2]SURGERY OF THE FOOT. By Henri L. DuVries, M.D. Foreword by Karl A. Meyer, M.D. Introduction by Edward L. Compere, M.D. 494 pages, 403 illustrations. $12.50. St. Louis: The C. V. Mosby Co., 1959.

[3]TRANSPLANTATION OF TISSUES; SKIN, CORNEA, FAT, NERVES, TEETH, BLOOD VESSELS, ENDOCRINE GLANDS, ORGANS, PERITONEUM, CANCER CELLS. Edited by Lyndon A. Peer, M.D. With 12 contributors. Vol. II. 690 pages, 252 illustrations. $20.00. Baltimore: The Williams & Wilkins Co., 1959.

progress in transplantation, it should prove very valuable. The material is quite up to date. A number of the references in the text are to publications within a year of the date of publication, and many within a period of 2 years of publication. —*Bradford Cannon.*

IN THE FOREWORD of the volume entitled *Cardiac Arrest and Resuscitation*[4] by Hugh E. Stephenson, Jr., the late Robert S. Dinsmore stated: "I believe all surgeons and anesthesiologists owe Dr. Stephenson great praise for this volume." This reviewer heartily agrees as well as recommends and urges each doctor, regardless of his specialty, to read and reread this most comprehensive informative study and review concerning all known phases of the etiology, the prevention, the treatment, and the sequelae of cardiac arrest.

The first sentence in the preface should awaken all doctors to the importance of the problem: "The annual deaths from sudden cardiac arrest, as they relate to surgery and anesthesia, alone, number more than the annual deaths from a combination of poliomyelitis, multiple sclerosis, scarlet fever, typhoid, diphtheria, and several of the other commonly mentioned diseases."

"In this book the author attempts to bring together a concise summary of our present day knowledge on cardiac arrest and resuscitation." Stephenson, with those to whom he gives credit, has fulfilled his purpose excellently. The history, incidence, diagnosis, etiology, management of complications, prognosis, prevention, care of the postresuscitative patient, and neurological sequelae each are considered in individual chapters. The review of the literature and the bibliography are extensive and detailed.

The author is to be commended. The study of his book and application of its advice, by the profession, will result in the saving of many lives each year.

—*Egbert H. Fell.*

THE MONOGRAPH entitled *Chronic Subdural Hematoma*[5] is unique in that it represents a study undertaken by a surgeon whose training is in general and orthopedic surgery but who developed interest in craniocerebral injuries while on the neurosurgical service at the University Hospital in Oslo, Norway, from July 1947 to December 1952.

The author has briefly but adequately surveyed the literature on each phase of the history, diagnosis, and treatment of subdural and cerebral hemorrhages. The material on which this study is based consists of 37 chronic subdural hematomas and hygromas, 9 acute subdural hemorrhages, 2 subdural blood accumulations, 10 epidural hemorrhages, and 13 intracerebral hemorrhages of various causes. The history, etiology, pathology, and anatomy are briefly but adequately presented. Other than that, the monograph does not bring any new thoughts or diagnostic or therapeutic points to attention. It does summarize, very briefly, and brings to attention the important symptoms, diagnostic points, and methods of treatment. The monograph must be considered a worthy addition to neurosurgical literature and is particularly recommended for those whose experience with subdural hematomas is limited.

—*David Cleveland.*

IN THE NEW VOLUME X OF *Archivio "Putti"*[6] are presented a number of excellent papers by Italian orthopedists, anatomists, and histologists. Color prints are used profusely.

"Histochemical Investigations of Giant Cell Tumors" by Pais and Baruffaldi portrays exhaustive histochemical studies of the enzymes, mucopolysaccharides, nucleic acids, and lipids in 15 cases. Nine of the tumors were considered benign giant cell tumors and 6 were malignant. The terms "fibroma with osteoclasts" (myeloplaxes) and "sarcoma with osteoclasts" are favored by the authors to designate the benign and malignant forms of giant cell tumors respectively. Mucopolysaccharides appeared to be more abundant in the giant cells of benign tumors than in the malignant forms. The greater abundance of mucopolysaccharides in the giant cells of benign tumors indicates that these cells are more mature, whereas the absence of mucopolysaccharides in the giant cells of malignant tumors indicates immaturity. According to the authors, the histochemical differences in the giant cells may be important in the estimation of benignity or malignancy of the tumor.

Bertolin and Fonzone studied the "Biochemical Alterations in the Achilles Tendon and the Intervertebral Disc of Man" in relation to aging. Decrease in water content and in mucopolysaccharides was observed in the last decades of life.

Under the title "Histological Changes of the Insertion of the Tendo Achillis into the Os Calcis in Senility" a very extensive study is reported by Grilli of the manner of insertion of the tendo achillis into the os calcis and of the degenerative changes of this insertion which occur with age. A chondroid transformation of the tendinous tissues is often found with degenerative changes similar to those observed in degenerative joint disease. Spur formation occurs by ossification in the calcified tendinous tissue.

"Histochemical Studies of Normal and Pathological Synovial Membrane" were made by Rinonapoli and Sanguinetti. Carbohydrates and mucopolysaccharides were found to be very scarce in the synovial membrane: but these substances were present in the perivascular connective tissues. They were completely absent in the tuberculous granulomas. On the other hand, mucopolysaccharides were always abundant in the synovia of patients with rheumatoid arthritis and in smaller quantities in nonspecific arthritis.

Lunardo and Bastiani present three articles on "The Action of Different Sugars on the Osteoporosis

[4]CARDIAC ARREST AND RESUSCITATION. By Hugh E. Stephenson, Jr., M.D. 378 pages, 31 illustrations. $12.00. St. Louis: C. V. Mosby Co., 1958.

[5]CHRONIC SUBDURAL HEMATOMA; WITH PARTICULAR REFERENCE TO THE DIAGNOSIS. A CLINICAL, ROENTGENOLOGICAL AND ELECTROENCEPHALOGRAPHICAL STUDY. By Ragnar Nordlie. 164 pages, illustrated. Oslo, Norway: John Grundt Tanum Forlag, 1958.

[6]ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Directed by Prof. C. Pais (Genova), C. Casuccio (Padova), and O. Scaglietti (Firenze). Edited by L. Gui (Bologna). Vol. X. 1 Semestre 1958. 579 pages, illustrated. Firenze: Edizioni Scientifiche dell "Istituto Ortopedico Toscano," 1958.

and Growth Retardation Observed in Experimental Diabetic rats." The diabetes was produced by intraperitoneal administration of alloxan. It appears that the osteoporosis and the growth arrest in diabetic rats is due to a decrease in the capacity of the tissues to utilize the carbohydrates. The insulin does not have a direct effect on the osteoblasts but rather it causes a better utilization of the carbohydrates at the tissue level. On the other hand, adenosine triphosphoric acid or galactose administered to young rats with experimental diabetes does not correct the retardation of growth.

"Architecture and Structure of the Blood Vessels in the Fibrous Tissue of the Joints of Man" is the title of a paper by Scapinelli. A great number of arteriovenous anastomoses of various types were observed in the fibrous tissue of joints; in the same areas capillaries were scarce.

Caretto, working with Amprino at the University of Bari wrote a very careful study of "The Newly Formed Bone Matrix in Long Bones of Various Species of Mammals." Histologic, histochemical, microradiographic, and autoradiographic techniques were used.

"Experimental Studies on Stimulation of the Epiphyseal Plate with Changes of the Local Circulation" are presented by Stringa. By means of a polyethylene sheath introduced into the tibial metaphysis of young rabbits the diaphysial blood supply to the epiphysial plate is interrupted. An overgrowth of 2 to 5 millimeters of the tibia occurs during the first and second weeks. This increase in length of the tibia remained the same during the 20 week duration of the experiments.

The "Relationship between Anomaly of Development of the Femoral Neck and Secondary Subluxation of the Hip" is discussed by Sebastiani. Failure of good development of a reduced congenital dislocation of the hip may be due to various causes, such as osteochondritis of the femoral head, primitive hypoplasia of the acetabular roof, or anteversion of the femoral neck. In this material the author studied 52 cases in which after reduction, either excessive varus or excessive valgus of the femoral neck developed.

"Cysts of the Medial Meniscus of the Knee" are discussed by Travaglini. Eight cases are reported which were observed in the "Istituto Ortopedico Toscano" of Florence. These cysts, which are much less common than cysts of the lateral meniscus, appear to be due to a colloid degeneration of the fibrocartilage, probably of traumatic origin.

Monesi and Betini present a comprehensive monograph on "Histochemical Investigations Applied to Physiopathology of Bone Tissue." Current techniques used in histochemistry are described and evaluated as to their importance in bone and cartilage tissues. The histochemistry of endochondral and intramembranous ossification is particularly studied and illustrated with beautiful color reproductions.

A very extensive orthopedic bibliography is found in the last part of this book. —*I. V. Ponseti.*

WELL PRESENTED on excellent paper and beautifully bound is the volume by R. Michel-Béchet entitled *Atlas de techniques chirurgicales*.[7] Despite the fact that it is limited in content to usual operative procedures of the neck, thorax, abdomen, and pelvic organs, it is larger and more extensively illustrated than most American "picture" books which illustrate operative techniques. The author sets out to produce a French counterpart of Cutler and Zollinger's book on surgical technique and does an excellent job. While the illustrations are better, the book has the same general defects of its American predecessor. It is quite large and, therefore, can be used only as a reference copy. Technical and anatomic aspects of operative procedures are illustrated without discussion of preference or reasons for performing one procedure over another. No special claims are made as to its possible usefulness to any one group. The illustrations and their continuity speak for themselves in clarity and precision.

Steps in operations are well presented and with sufficient added semidiagrammatic reproductions to add understanding. There is very little accompanying text but it is simple and utilizes terminology which is standard surgical and anatomic nomenclature, so that one with a limited knowledge of French can easily follow the brief text. There is an adequate amount of blank spaces between the cuts for discussion of the objectives of the operative procedures. As it is, the illustrations provide sufficient technical direction for the American resident surgeon.

The operative procedures illustrated are standard and commonly accepted. Techniques described by American as well as European surgeons are included, and one cannot help noting their similarity. Principles underlying various suture techniques are well illustrated. Intestinal anastomosis with a Murphy button or its French counterpart by Jaboulay is presented. While this may be only of historical interest, it is presented along with other standard methods. It might be somewhat difficult to find such equipment in a modern hospital should one wish to learn this technique.

The usefulness of this book is limited by its size and weight. It weighs 10 pounds and is of awkward dimensions. Even the sturdiest of surgical residents would find it difficult to carry about for study. As a volume to have accessible in the surgical residents' reading room, it ought to be of value for comparison of techniques as well as a general review of anatomic relationships. —*Charles G. Johnston.*

THE NEW SECOND EDITION of *The Physiopathology of Cancer*[8] represents a further improvement upon a most helpful and stimulating compilation in the general field of neoplastic disease. This rather bulky text of 1180 pages is the product of 32 widely known authorities and contains a great deal of significant data and critical analyses of the most recent oncologic develop-

[7] ATLAS DE TECHNIQUES CHIRURGICALES; LES GRANDES TECHNIQUES; COU, THORAX, ABDOMEN, CHIRURGIE PELVIENNE. By R. Michel-Béchet. 579 pages, 1,125 illustrations by P. Contier. 25,000 fr. Paris: G. Doin & Cie, 1958.

[8] THE PHYSIOPATHOLOGY OF CANCER. By 32 authors. Edited by Freddy Homburger, M.D. Foreword by Joseph C. Aub, M.D., Sc.D. 2nd ed. 1180 pages, 189 illustrations. $32.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1959.

ments. There have been extensive revisions and numerous additions to make this edition completely up to date. There are 7 new chapters and 8 new contributors, to say nothing about the changes and new illustrations that have been added to the former text material. The bibliographies at the end of each chapter are quite extensive and worthy of particular mention.

The general organization of the text into 4 main sections remains the same. In part 1, Biology, this reviewer was much impressed by the new chapters on "Genetics in Neoplasia," "Heterologous Transplantation," and "Uses of Tissue Culture in the Study of Malignancy." Robert Mellors' new contribution to "Cancer Cytochemistry and Histochemistry" in the second edition represents a particularly valuable addition, not only because it fills a gap previously noted in the first volume but it affords both the serious student and clinician an opportunity to become acquainted with a very exciting aspect of basic chemical analysis in neoplastic disease. Shimkin's chapter on the "Natural History of Neoplastic Disease," while not necessarily new information, is a foundation type of contribution for the section on clinical investigation and as such it rounds out the text a great deal. Although various specific and other less well documented aspects of the general problem of "host resistance" are mentioned, one is impressed with the fact that a separate section on the immunology of cancer should have been included for the sake of completeness.

If we are to find fault with this edition, it must be pointed out that the section on steroid hormone metabolism is woefully lacking as regards surgical ablation of endocrine influences. While it is admittedly an area of clinical investigation in which firm conclusions are still to be made, this is truly one area in which surgery has proved capable of altering the physiopathologic or predictable growth aspects of certain "endocrine dependent" cancers. Documentary evidence to support these variations is now available, but adequate reference to this phenomenon is lacking in this text.

The fourth and last section of this edition pertaining to the practical applications of recent advances has been reduced to some extent but this is to the editor's credit. As in the previous edition, the chapter on applied radiation therapy contained the only reference to the indications and value of surgical excisional therapy for malignant disease. Due to the limitations of space one appreciates that complete coverage could not be realized, but for the sake of balance, it seems strange that a surgeon is not represented in this section. While the radiotherapist does give credit to the general observation that "there are some neoplasms which can only be cured by surgery" the over-all orientation is such that perhaps the clinically inexperienced reader might very well conclude that our modern effective oncologic therapeutic armamentatrium consists mainly of radiotherapy. While this is admittedly untenable, a detailed analysis of this section and how this impression can be created is very interesting. For example, it is stated that there are about 350 new cases of cancer per 100,000 population per annum in this country. In the previous edition, the figure was 225 new cases, using the same identical reference! The author further estimates that radiation therapy is used in some form in the care of about 60 per cent of all cancer patients and proceeds to give a reference from the year 1941. Emphasis is then placed not upon actual curative value of radiotherapy but rather its excellence in obtaining cosmetic and functional results with less physical strain, in addition to reduced economic and psychic stress for the patient. On the other hand, surgical results are quoted mostly from an era other than the present and this adds little to the value of the text. The very important clinical problem of palliative care is barely mentioned and certainly deserves more coverage. While radiotherapy and surgery are often presented to the reader as of almost equal therapeutic value, it should be noted that the author is careful to spell out the fact that certain neoplasms just do not respond to radiotherapy. Forearmed with such information, the practical modern clinician can now be expected to accomplish much more in regard to comfortable patient survival by means of his proper selection of the more efficacious therapeutic modality.

—*Walter W. Carroll.*

A CONCENTRATED REVIEW of the literature concerning disorders and injuries of colon and rectum, exclusive of malignant neoplasms except when required in differential diagnosis, is presented in the volume entitled *Die Krankheiten und Verletzungen des Dickdarms und Mastdarms*.[9]

Professor Wildegans has reviewed the literature extensively, not stopping at the Iron Curtain, and has presented his material without the dogmatism characteristic of many textbooks. In the familiar sequence of etiology, pathogenesis, symptoms, pathophysiology, management, and complications the experiences of many contributors are related. Illustrative cases and results of therapy are discussed. Historical views and methods are mentioned as are current theories (1957). Their development, along with progressively improving figures showing results when applicable, is presented.

The twenty-six page bibliography at the end of this excellently bound volume is grouped alphabetically under the major headings of the text. This eliminates cluttering the text with reference numbers and considerably facilitates the search for the source of information.

The terminology is precise, and even a semanticist will enjoy the exactitude with which differential levels of the intestine are designated, namely with reference to their relative proximity to mouth or anus, as contrasted to the nebulous but commonly used "proximal" and "distal" end of the colon.

The section on congenital malformations of the colon and rectum includes a description of the embryogenesis of the small bowel as well, and it contains fifty per cent of the book's illustrations, most of which are either schematic drawings or roentgenograms.

[9]DIE KRANKHEITEN UND VERLETZUNGEN DES DICKDARMS UND MASTDARMS (OHNE BOESARTIGE GESCHWUELSTE). By Prof. Dr. Hans Wildegans. 355 pages, 57 illustrations. Stuttgart: Ferdinand Enke Verlag, 1959.

Injuries to the colon and adjacent structures are described under several subheadings covering penetrating and nonpenetrating trauma, and including perforations secondary to parasitic infestations. This is one of the first postwar reviews of war injuries in the German armies.

Diverticulosis and its complications are outlined in detail, and statistics and numerous references are given for further review. The section on inflammatory lesions elaborates on postoperative pseudomembranous enterocolitis and current thoughts on its predisposing factors.

Specific inflammations ranging from typhoid fever and the dysenteries, both bacillary and amebic, to tuberculosis—still prevalent in remarkably high numbers in Europe—actinomycosis, syphilis, and schistosomiasis of the bowel, are discussed, as well as the most recent therapy.

Three chapters are devoted to pneumatosis cystica and benign tumors of the bowel, including nonspecific granulomas and endometriosis.

There is an excellent elaboration on the multitude of lesions capable of producing obturation or compression of the bowel. All possible and several potential sites of external and internal herniation of the large bowel are mentioned, with cross references to the section on congenital malformations. Volvulus, intussusception, the paralytic ileus, and thrombosis and embolism of mesenteric vessels are all discussed.

In addition to congenital and postoperative rectal strictures, the author has described the inflammatory variety with particular reference to complications of lymphogranuloma inguinale.

Historical measures used to treat the prolapsed rectum are listed, and the reasons for failures are recounted. Individualized therapy is indicated, depending on the type and degree of prolapse and aiming at any or all of the measures designed to decrease the size of the anal ring, repair of the pelvic floor, reduction of the depth of Douglas' pouch, and suspension of the endgut, with or without resection of redundant rectosigmoid.

There is a detailed discussion of the diagnosis and management of pectenosis, anal pruritus, fissure, fistula, and incontinence, as well as the injection and surgical treatment of hemorrhoids.

In summary, this volume is an excellent outline and reference book, and readers will be interested in the tremendous amount of material reviewed. Due to the clarity of the text and the predominance of Latin nomenclature, the English-speaking student of the subject with but reading knowledge of scientific German will benefit, no matter how extensive or quick access to the literature he may desire. This contribution is not intended to be a textbook for the neophyte, but it should be a good guide for further study. —*Gunars Graudins.*

IN THE BOOK chiefly devoted to the study of *Gynecologic Endocrinology*,[10] most of the chapters are written with extreme clarity and contain a considerable amount of information. The material is presented in relatively simple form making the volume readily understandable. Beginning with a rather complete review of the anatomy, histology, and physiology of the female reproductive system, the book includes a discussion of the effect of oxytocin on milk secretion and on the action of the various hormones concerned with cyclic changes. The book is enriched with chapters concerning clinical aspects and diagnostic procedures, ending with a chapter listing endocrine preparations which are commercially available. The index is satisfactory and the references listed at the end of each chapter will prove useful. For those who desire a text to review the advances in gynecologic endocrinology, this book will serve adequately. —*Robert B. Greenblatt.*

THE SECOND EDITION of *Pathology*[11] by Herbut most adequately fulfills the prerequisites required to be of value to the medical student in his introductory course in this subject or to the practicing physician who seeks a thorough review in the field of pathology.

The author judiciously opened this text with a section devoted to an orientation in, evolution of, and purpose of pathology. There is a succinct chapter on autopsy. Some of this space might have been allotted to the aspects of surgical pathology.

One rather admirable point is the brevity of space alloted to principles. Thus, the student quickly faces the systems which usually are more pleasant reading as well as more informative. The author has divided the contents of the chapters according to organ or organ-system, each of which is prefaced by a short section that is devoted to the pathologic physiology of the subject at hand. This, from the student's or physician's point of view, is of value as a review of the anatomy and physiology of the organ to be studied. Moreover, by the insertion of the clinical manifestations, treatment, and prognosis of the entity in question, the author has unveiled some of the problems which the student will face in the future or has recapitulated them for the practicing physician.

The text has adequate visual aids in the form of photographs and photomicrographs and contains adequate references so that it is of use to those in search of more extensive works.

As to the actual material contained in the text, it is as thorough and complete as one would wish for an introductory work or one to be used as a review of the subject. The author's style is clear, fresh, and extremely readable; these in combination appeal to the medical student already burdened with many stale encyclopedic works.

One minor criticism of the text is the addition of 288 pages, with a resultant total of 1500 pages making it somewhat too cumbersome. —*M. C. Wheelock.*

AN AUTOBIOGRAPHY by Rear Admiral Herbert Lamont Pugh, *Navy Surgeon*,[12] is an entertaining mixture of salty humor, candor, and precise observation, pre-

[10]GYNECOLOGIC ENDOCRINOLOGY. By Gardner M. Riley, Ph.D. Foreword by Norman F. Miller, M.D. 330 pages, 72 illustrations. $8.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1959.

[11]PATHOLOGY. By Peter A. Herbut, M.D. 2nd ed. 1516 pages 1506 illustrations and 6 color plates. $18.50. Philadelphia: Lea & Febiger, 1959.

[12]NAVY SURGEON. By Herbert Lamont Pugh. 459 page illustrated. $5.00. Philadelphia and New York: J. B. Lippincott Co., 1959.

senting a close-up view of one man's contact with recent American history. From a humble beginning on a farm in the hill country of Virginia, Pugh's memories carry the reader through the three periods of his life: "The Green Years," "Heyday," and "Vintage Years."

The period referred to as "The Green Years" is primarily the story of his boyhood, beginning in 1895 and ending with his entry into the U. S. Navy in 1923. The affectionate description of his introduction to higher learning in a one-room school, of his early companions, including "Rover," of hog-killing and what is meant by "chitterlings" and how they are prepared, of the innumerable minutiae so important in the life of a boy—all of these unfold before the reader with a sincerity and simplicity that is completely captivating.

The subsequent sections of the book deal with Pugh's travels over "millions of miles to all parts of the earth," his duties in World War II, his rise to increasingly important and increasingly exacting assignments, culminating in his experiences as Surgeon General of the Navy; then the cruel heart attack, deceleration, the second heart attack, and retirement —return to the hills of Virginia and life within 10 miles of "Jack's Hollow," his birthplace.

"Thus I come to the end of my odyssey. . . . I have no dread of advancing years. . . . I would suggest to those who are growing old that they read Longfellow's 'Morituri Salutamus.' I can appreciate now . . . the thought . . . from that poem:

'And as the evening twilight fades away
'The sky is filled with stars invisible by day.' "

—C. A. Broaddus, Jr.

THE MAGNIFICENT book *Surgery of the Ear*[13] is truly a monumental contribution that reflects George Shambaugh's sincere dedication to otology. Without doubt, it will be recognized as the classical reference book for otologic surgery for many years to come.

The contents are divided into: I. Introduction to Surgery of the Ear, II. Surgery of Infections of the Ear; III. Surgery of Deafness, IV. Surgery of the Facial Nerve, Endolymphatic Hydrops, and Tumors of the Ear. In the first part, the developmental anatomy of the ear, the surgical anatomy of the temporal bone, and the radiologic examination of the temporal bone are described clearly and concisely. Excellent reproductions of roentgenograms are made even more valuable by the accompanying labeled line drawings. In the second part, the discussion of otitis media and mastoiditis is concise, logical, and obviously written with a thorough and complete understanding of the pathologic processes involved. In part III, dealing with the surgery of deafness, Shambaugh perhaps reaches his greatest heights as teacher and author. His discussion of hearing and the diseases producing deafness and his detailed description of various surgical procedures utilized to improve impaired hearing are of the finest.

The entire volume is generously and superbly illustrated. Beautifully executed drawings depict every stage of many of the operations described. The many colored reproductions are of unusual excellence.

Exhaustive lists of references are placed at the end of each chapter. The index seems most complete allowing for prompt location of any desired item.

Quite obviously, no expense has been spared in illustrating, printing. and binding this superb volume. A brief review cannot do it justice. It is recommended strongly that *Surgery of the Ear* be studied by every practicing otologist and that it be utilized freely by teachers, particularly in residency training programs.

—James B. Maxwell.

VOLUME VII is one of eight volumes which comprise the *Treatise of Surgical Technique*.[14] The authors are distinguished French surgeons.

The treatise discussed "all the surgical techniques" involved in the treatment of diseases of the liver, pancreas, spleen, omentum, mesentery, vessels, and nerves of the abdomen. Included is a discussion of emergency laparotomies and drainage of abscesses.

This is a practical book, the purpose of which is also to indicate how each surgical procedure is to be carried out once it has been decided upon. It is well illustrated and many of its chapters and illustrations are entirely new. There is a bibliography at the end of each chapter and an alphabetical index at the end of each volume.

Particularly well documented are new chapters on portacaval anastomosis, resection of aneurysm of the abdominal aorta, and dorsolumbar sympathectomy.

—Rene Joyeuse.

THE NEW tenth edition of Cecil and Loeb's *A Textbook of Medicine*[15] exceeds all other editions in content, make-up, general appearance, and apparent usefulness to the student and practitioner of medicine. The editors have been assisted by 3 associate editors and 171 co-authors, each an authority in the field covered in his essay.

More than eight hundred diseases and disorders are discussed, and there are thirty-six articles on subjects not included in previous editions. These include adenoviral and echoviral infections, high altitude sickness, salicylate poisoning, carcinoidosis, steroid physiology and metabolism, hyperaldosteronism, and the syndromes of Tietze and Marfan. These subjects are adequately presented without sacrifice of other material by the use of a new, clearer type which permits an increase in the text without an additional number of pages.

The editors quite properly direct the attention of the reader to the foreword by Dane W. Atchley. This addition expresses the timeless philosophy so essential

[13] SURGERY OF THE EAR. By George E. Shambaugh, Jr., M.D. 769 pages, 326 illustrations. Philadelphia and London: W. B. Saunders Co., 1959.

[14] TRAITE DE TECHNIQUE CHIRURGICALE. By B. Fey, P. Mocquot, S. Oberlin, J. Quenu, P. Truffert, M. David, M. Iselin, R. Dossot, R. Dubau, Ch. Dubost, Ct. Dubost, J.-J. Galey, Y. Longuet, J. Loygue, J. Mathey, R. Palmer, J. Perrotin, J.-C. Rudler, G. Thomeret, and J. Varangot. 2nd rev. ed. Vol. VII, Abdomen. 769 pages, 526 illustrations. 7,200 fr. Paris: Masson et Cie, 1959.

[15] A TEXTBOOK OF MEDICINE. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Sc.D., D. Hon. Causa., LL.D. Assisted by Alexander B. Gutman, M.D., Ph.D., Walsh McDermott, M.D., and Harold G. Wolff, M.D. 10th ed. 1665 pages, 182 illustrations. Philadelphia and London: W. B. Saunders Co., 1959.

for successful communication between doctor and patient. It should be read before proceeding with the main portion of the volume as it expresses in a thousand words the "art" of medicine.

Each discussion is accompanied by important references to the literature to give the reader an opportunity to explore the subject further in the library. Unusual emphasis has been given to the index, and this also will enhance the value of the book to the student and practitioner.

This extensively revised edition is filled with important details for effectively understanding, diagnosing, and managing most of the medical problems met in day to day practice. It should be of great value to the practitioner of medicine, as well as to the medical student. —*George C. Turnbull.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Anatomy of the Human Body. By Henry Gray, F.R.S. Edited by Charles Mayo Goss, M.D. 27th ed. 1458 pages, 1174 illustrations. $17.50. Philadelphia: Lea & Febiger, 1959.

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., Sc.D. (Hon.), F.A.C.P., and W. Proctor Harvey, M.D. 2nd ed. 657 pages, 660 illustrations. $11.00. Philadelphia and London: W. B. Saunders Co., 1959.

Disorders of the Temporomandibular Joint; Diagnosis, Management, Relation to Occlusion of Teeth. By Laszlo Schwartz, D.D.S. and 18 contributors. 471 pages, 458 illustrations. $15.00. Philadelphia and London: W. B. Saunders Co., 1959.

The Law of Medical Practice. By Burke Shartel and Marcus L. Plant. 445 pages. $12.50. Springfield, Ill.: Charles C Thomas, 1959.

The Contributions of Dr. C. C. Guthrie to Vascular Surgery. By Samuel P. Harbison, M.D., and Bernard Fisher, M.D. Blood Vessel Surgery and Its Applications. By Charles Claude Guthrie, M.D., Ph.D. (A Reprint) 83 pages, 115 illustrations. $7.50. Pittsburgh: University of Pittsburgh Press, 1959.

The Pharmacology and Clinical Use of Diuretics. By Carroll A. Handley, Ph.D., and John H. Moyer, M.D. 194 pages, illustrated. $6.00. Springfield, Ill.: Charles C Thomas, 1959.

Hypnosis in Anesthesiology. By Milton J. Marmer, M.D., M.Sc.Med. (Anes.) Foreword by John B. Dillon, M.D. 150 pages. $6.75. Springfield, Ill.: Charles C Thomas, 1959.

Clinical Disorders of Hydration and Acid-Base Equilibrium. By Louis G. Welt, M.D. 2nd ed. 336 pages, illustrated. $7.00. Boston and Toronto: Little, Brown and Co., 1959.

Clinical Prosthetics for Physicians and Therapists; a Handbook of Clinical Practices Related to Artificial Limbs. By Miles H. Anderson, Ed.D., Charles O. Bechtol, M.D., and Raymond E. Sollars. 393 pages, illustrated. $10.50. Springfield, Ill.: Charles C Thomas, 1959.

Pediatric Pathology. By Daniel Stowens, M.D. 676 pages, 374 illustrations. $20.00. Baltimore: The Williams & Wilkins Co., 1959.

Sechzig Jahre Medizinische Radiologie; Probleme und Empirie. By Hans R. Schniz, Prof. Dr. Med. Dr. Rer. Nat. h.c. 275 pages, 86 illustrations. $4.65. Stuttgart: Georg Thieme, 1959.

The Surgical Treatment of Facial Injuries. By Varaztad Hovhannes Kazanjian, C.M.G., D.M.D., M.D., F.A.C.S., D.Sc. (Hon.), and John Marquis Converse, M.D., F.A.C.S. 2nd ed. 1110 pages, 1155 illustrations. $22.00. Baltimore: The Williams & Wilkins Co., 1959.

Mazer & Israel's Diagnosis and Treatment of Menstrual Disorders and Sterility. By S. Leon Israel, M.D. 4th ed. 666 pages, 147 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Brothers, 1959.

Strahlenbiologie; Grundlagen und Ergebnisse. By Prof. Dr. Hedi Fritz-Niggli. 379 pages, 168 illustrations. $15.50. Stuttgart: Georg Thieme, 1959.

Relaxation and Exercise for Natural Childbirth. By Helen Heardman. 2nd ed. 31 pages, 20 illustrations. $.75. Edinburgh & London: E. & S. Livingston Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

Synopsis of Gynecology. By Robert James Crossen, M.D., Daniel Winston Beacham, M.D., and Woodard Davis Beacham, M.D. 340 pages, 106 illustrations, including 1 in color. $6.50. St. Louis: The C. V. Mosby Co., 1959.

Cinco ensayos sobre la vida sexual. By Dr. José Chelala. 146 pages. Habana, Cuba, 1959.

A Text-Book of X-Ray Diagnosis by British Authors in Four Volumes. Edited by S. Cochrane Shanks, C.B.E., M.D., F.R.C.P., F.F.R., and Peter Kerley, C.V.P., C.B.E., M.D., F.R.C.P., F.F.R., C.M.R.E. 3rd ed. Vol. IV. 714 pages, 735 illustrations. $21.00. Philadelphia and London: W. B. Saunders Company, 1959.

The Foot and Ankle; Their Injuries, Diseases, Deformities, and Disabilities. By Philip Lewin, M.D., F.A.C.S., F.I.C.S. 4th ed. 612 pages, 339 illustrations. Special drawings by Harold Laufman, M.D., F.A.C.S. $14.00. Philadelphia: Lea & Febiger, 1959.

Childbirth Without Fear; the Principles and Practice of Natural Childbirth. By Grantly Dick-Read, M.D., M.D. (Cantab.) 2nd ed. 361 pages, illustrated. $4.00. New York: Harper & Brothers, 1959.

Human Nutrition and Dietetics. By Sir Stanley Davidson, B.A., Cantab., M.D., F.R.C.P. Ed., F.R.C.P. Lond., M.D. Oslo, A. P. Meiklejohn, M.A., B.Sc., D.M.Oxon, M.R.C.P. Lond., and R. Passmore, M.A., D.M.Oxon. Foreword by Lord Boyd Orr, D.S.O., M.C., LL.D., F.R.S. 844 pages, illustrated. $15.00. Baltimore: The Williams & Wilkins Co., 1959.

Cancer of the Breast. Compiled and edited by Willard H. Parsons, M.D., F.A.C.S. Foreword by Warren H. Cole, M.D., F.A.C.S. 232 pages, illustrated. $7.50. Springfield, Ill.: Charles C Thomas, 1959.

Clinical Orthopaedics. Editor-in-Chief Anthony F. DePalma with the assistance of the Associate Editors, The Board of Advisory Editors, and The Board of Corresponding Editors. Albert B. Ferguson, Jr., Guest Editor. No. 14, Summer, 1959. 193 pages, illustrated. $7.50. Philadelphia and Montreal: J. B. Lippincott Co., 1959.